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(54) **Title**: USE OF NK-1 RECEPTOR ANTAGONIST SERLOPITANT IN PRURITUS

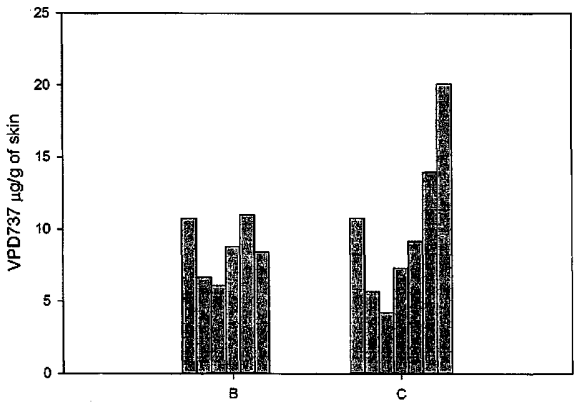


FIG. 4

(57) **Abstract**: The invention relates to methods for treating pruritus with NK-1 receptor antagonists such as serlopitant. The invention further relates to pharmaceutical compositions comprising NK-1 receptor antagonists such as serlopitant. In addition, the invention encompasses treatment of a pruritus-associated condition with serlopitant and an additional antipruritic agent, and the use of serlopitant as a sleep aid, optionally in combination with an additional sleep-aiding agent.

USE OF NK-1 RECEPTOR ANTAGONIST SERLOPITANT IN PRURITUS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to and the benefit of US Patent Application No. 13/925,509 and US Provisional Patent Application No. 61/838,784, both filed on June 24, 2013.

TECHNICAL FIELD

[0002] The invention relates to methods for treating acute or chronic pruritus with an NK-1 receptor antagonist. The invention further relates to pharmaceutical compositions comprising an NK-1 receptor antagonist.

BACKGROUND OF THE INVENTION

[0003] Pruritus, or itch, is an uncomfortable skin sensation that provokes a desire to scratch. Although itch may be acute, for example, from an insect sting, chronic pruritus originates from many different causes. It is a seriously debilitating condition, comparable to chronic pain, which negatively impacts quality of life.

[0004] Chronic pruritus affects millions of people worldwide, although solid epidemiological data is very limited. For example, one study reported that 8-10% of the population of Oslo suffer from chronic pruritus from all causes (F. Dalgard *et al.*, *J. Investig. Dermatol. Symp. Proc.*, 2004, **9**(2):120–5). Patients with certain diseases and conditions report high incidences of chronic itch, including those with psoriasis (78-84%), Hodgkin's disease (25-35%), dialysis patients (22%), and polycythaemica vera (48%) (M. Metz and S. Ständer, *CME Dermatol.*, 2008; 3(3):124–143). Chronic pruritus is also a prevalent symptom in cutaneous T-cell lymphoma (68-93%), a disease that includes mycosis fungoides and Sézary syndrome (N. Meyer *et al.*, *Acta Derm. Venereol.*, 2010, **90**:12-17). Pruritus is the most common dermatological complaint in elderly patients (S. Beauregard and B. A. Gilchrest, *Arch. Dermatol.*, 1987, **123**:1638-43). Itch is often the side effect of certain drugs, such as EGF receptor antagonists.

[0005] Antihistamines can sometimes effectively treat itch due to acute urticaria, but many chronic pruritic diseases respond poorly to conventional H1 receptor antagonists (Tey H.L. and G. Yosipovitch; *Br. J. Dermatol.*, 2011, **165**(1):5-17). In addition to marginal efficacy, antihistamines can also cause intolerable drowsiness. Other current therapies possess various limitations. For example, anticonvulsants such as gabapentin inhibit spinal mechanisms in the perception of itch, but their use is limited due to their slow onset of action (5-6 weeks) (Metz and Ständer, 2008). Opiate receptor

antagonists such as naloxone, nalmefene, and naltrexone decreased pruritus symptoms in patients with liver and kidney disease, although significant central nervous and gastrointestinal side effects occurred (Metz and Ständer, 2008; N. V. Bergasa *et al.*, *Hepatology*, 2006, **44**(5):1317-23).

[0006] Substance P, the endogenous ligand for the neurokinin-1 (NK-1) receptor, is a significant mediator of pruritus (T. Andoh *et al.*, *J. Pharmacol. Exp. Ther.*,1998, **286**:1140-5). Intradermal injection of substance P elicits an itch sensation in human subjects, and an associated itch response in mice. The substance P-induced itch–associated response in mice is not inhibited by antihistamines (B. Amatya *et al.*, *Skin Pharmacol. Physiol.*, 2010; **23**:133-138; C. Weidner *et al.*, *J. Invest. Dermatol.*, 2000, **115**:1015-1020). In an experiment designed to study the role of substance P in pruritus, Ohmura *et al.* reported that tachykinin NK-1 receptor antagonist, BIIF 1149 CL, inhibited scratching behavior in a picrylchloride-induced dermatitis model in NC/Nga mice (*Eur. J. Pharmacol.*, 2004, **491**:191–194; U.S. Patent Application No. 2003/100565).

[0007] Aprepitant (Emend®), an NK-1 receptor antagonist, is approved by the FDA for use in the prevention of chemically induced nausea and vomiting (emesis) after chemotherapy. Duval and Dubertret first reported that oral aprepitant (80 mg daily) had utility in treating pruritus in three patients with Sézary syndrome (*N. Engl. J. Med.*, 2009, **361**(14):1415-6). Torres *et al.* disclosed similar results (*J. Am. Acad. Dermatol.*, 2012; **66**(1):e14-5). Ständer *et al.* conducted a small, open-label study which demonstrated that aprepitant significantly decreased chronic pruritus caused by conditions such as atopic diathesis and prurigo nodularis. In this study, twenty previously untreatable patients were given a daily dose of 80 mg for 3 to 13 days. Eighty percent of the patients experienced a considerable reduction in itch intensity (S. Ständer, *et al.*, *PLoS One*, 2010, **5**:6, e10968). However, Wallengren conducted a follow-up double-blind study based on Ständer's work testing a single dose of topical aprepitant blended at a 5% concentration in a lipophilic vehicle in patients suffering from chronic pruritus of various etiologies. Although the drug was absorbed into the skin, the patients' itch was not alleviated (J. Wallengren, *Arch. Dermatol.*, 2012, **148**(8):957-9).

[0008] Although oral aprepitant is generally well-tolerated, it is extremely expensive, limiting its use in chronic pruritus (Tey, 2011). Further, aprepitant is a moderate inhibitor as well as an inducer of CYP3A4 and CYP2C9, indicating that drug-drug interactions with chemotherapeutic agents and corticosteroids must be considered (Torres, 2012). Mir and Coriat have suggested that the risk of drug-drug interactions with aprepitant is high because it can alter the activity of cytochrome P450 3A4 isoform (CYP-3A4), an enzyme involved in the metabolism of a range of commonly prescribed drugs, including tyrosine-kinase inhibitors, either inducing or inhibiting the CYP-3A4, depending on which drugs are given concomitantly. Tyrosine-kinase inhibitors do not induce frequent nausea and emesis;

therefore, clinical experience with concomitant administration of aprepitant and these drugs is scarce. Furthermore, the pharmacokinetics of tyrosine-kinase inhibitors varies widely between patients, and drug-drug interactions are common (O. Mir and R. Coriat, *The Lancet*, 2012, **13**:964-965). Thus, the need for additional, safe treatments for acute and chronic pruritus exists.

SUMMARY OF THE INVENTION

[0009] In one aspect, this invention provides a method of treating pruritus in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-4-(4-fluorophenyl)-1,3,3a,4,5,6,7,7a-octahydroisoindol-2-yl]cyclopent-2-en-1-one or a pharmaceutically acceptable salt, solvate or polymorph thereof. In one embodiment, the therapeutically effective amount comprises a dosage of 0.10 mg, 0.15 mg, 0.20 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg one or more times a day. In another embodiment, the therapeutically effective amount comprises a dosage of 0.25 mg, 1 mg, or 5 mg once a day. In a further embodiment, the therapeutically effective amount comprises a dosage of from about 0.1 mg to about 30 mg or from about 1 mg to about 7.5 mg. In another embodiment, the therapeutically effective amount is administered orally in the form of a tablet. In a further embodiment, the therapeutically effective amount is administered once a day at bedtime. In another embodiment, the therapeutically effective amount is administered once a day, once every other day, once every third day, once every fourth day, or once a week. In other embodiments, serlopitant is administered under a chronic dosing regimen. In some embodiments, a therapeutically effective amount of serlopitant is administered over a period of at least 2 weeks, 3 weeks, 1 month, 1.5 months, 2 months, 3 months, 4 months, 5 months, 6 months or longer.

[0010] In another aspect, this invention provides a method of treating pruritus whereby 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-4-(4-fluorophenyl)-1,3,3a,4,5,6,7,7a-octahydroisoindol-2-yl]cyclopent-2-en-1-one (serlopitant) or a pharmaceutically acceptable salt , solvate or polymorph thereof is administered to a patient in need of such treatment according to a schedule, wherein a least one loading dose is first administered, and, second, at least one therapeutically effect maintenance dose is administered. In one embodiment, the loading dose is five times, four times, three times, or two times the maintenance dose. In another embodiment, the loading dose is three times the maintenance dose. In a further embodiment, the loading dose is administered on day 1 and the maintenance dose is administered on day 2 and thereafter. In another embodiment, the loading dose and the maintenance dose are administered at bedtime. In another embodiment, the method further

comprises administering a second loading dose prior to administering the maintenance dose. In one embodiment, the loading dose is three times the maintenance dose and the second loading dose is two times the maintenance dose. In a further embodiment, the therapeutically effective maintenance dose is 0.10 mg, 0.15 mg, 0.20 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg administered one or more times a day. In another embodiment, the therapeutically effective maintenance dose comprises a dosage of 0.25 mg, 1 mg, or 5 mg administered once a day. In a further embodiment, the therapeutically effective maintenance dose comprises a dosage from about 0.1 mg to about 30 mg or from about 1 mg to about 7.5 mg. In another embodiment, the therapeutically effective maintenance dose is administered once a day, once every other day, once every third day, once every fourth day, or once a week. In other embodiments, serlopitant is administered under a chronic dosing regimen. In some embodiments, a therapeutically effective maintenance dose of serlopitant is administered over a period of at least 2 weeks, 3 weeks, 1 month, 1.5 months, 2 months, 3 months, 4 months, 5 months, 6 months or longer. In certain embodiments, serlopitant is administered orally.

[0011] In one aspect, this invention provides a pharmaceutical composition for the treatment of pruritus comprising 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-4-(4-fluorophenyl)-1,3,3a,4,5,6,7,7a-octahydroisoindol-2-yl]cyclopent-2-en-1-one or a pharmaceutically acceptable salt, solvate or polymorph thereof and a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition is formulated as a tablet comprising Compound 1 or a pharmaceutically acceptable salt, solvate or polymorph thereof and one or more diluents, disintegrants, surfactants or lubricants. In another embodiment, the composition comprises a capsule filled with a solution comprising Compound 1 or a pharmaceutically acceptable salt, solvate or polymorph thereof and an amphiphilic agent. In a further embodiment, the amphiphilic agent is a fatty acid ester of glycerol, propylene glycol or sorbitol. In another embodiment, the pharmaceutical composition comprises 0.10 mg, 0.15 mg, 0.20 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg of Compound 1 or a pharmaceutically acceptable salt, solvate or polymorph thereof. In another embodiment, the composition comprises 0.25 mg, 1 mg, or 5 mg of Compound 1 or a pharmaceutically acceptable salt, solvate or polymorph thereof.

[0012] In another aspect, this invention provides a method of treating acute or chronic pruritus in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-4-(4-fluorophenyl)-1,3,3a,4,5,6,7,7a-octahydroisoindol-2-yl]cyclopent-2-en-1-one or a pharmaceutically acceptable salt, solvate or polymorph thereof and a pharmaceutically

acceptable carrier. In one embodiment, the method involves treatment with a pharmaceutical composition formulated as a tablet comprising Compound 1 or a pharmaceutically acceptable salt, solvate or polymorph thereof and one or more diluents, disintegrants, surfactants or lubricants. In another embodiment, the method involves administration of a composition comprising a capsule filled with a solution comprising Compound 1 or a pharmaceutically acceptable salt, solvate or polymorph thereof and an amphiphilic agent. In a further embodiment, the amphiphilic agent is a fatty acid ester of glycerol, propylene glycol or sorbitol. In another embodiment, the method involves treatment with a pharmaceutical composition comprising 0.10 mg, 0.15 mg, 0.20 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg of Compound 1 or a pharmaceutically acceptable salt, solvate or polymorph thereof. In another embodiment, the composition comprises 0.25 mg, 1 mg, or 5 mg of Compound 1 or a pharmaceutically acceptable salt, solvate or polymorph thereof.

[0013] In a further embodiment, a pruritus-associated condition is treated by administration of serlopitant (Compound 1) and an additional antipruritic agent. In a still further embodiment, a sleep problem or disorder is treated by administration of serlopitant, optionally in combination with an additional sleep-aiding agent.

[0014] Other objects of the invention may be apparent to one skilled in the art upon reading the following specification and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0016] FIG. 1 depicts a synthetic scheme for serlopitant, Compound 1.

[0017] FIG. 2 illustrates a Franz diffusion cell for studying skin permeation of a drug *in vitro*.

[0018] FIG. 3 shows the cumulative release of serlopitant from topical formulations B and C into the receptor chamber of a Franz diffusion cell at various time points in an *in vitro* study of skin permeation.

[0019] FIG. 4 shows the amount of serlopitant (called "VPD737") retained in the skin at the end of the Franz diffusion cell study. Each bar represents ug of serlopitant/g of skin in 250 um skin layers. For each of topical formulations B and C, the bars from left to right represent the amount of serlopitant retained in skin layers from the stratum corneum to the dermis.

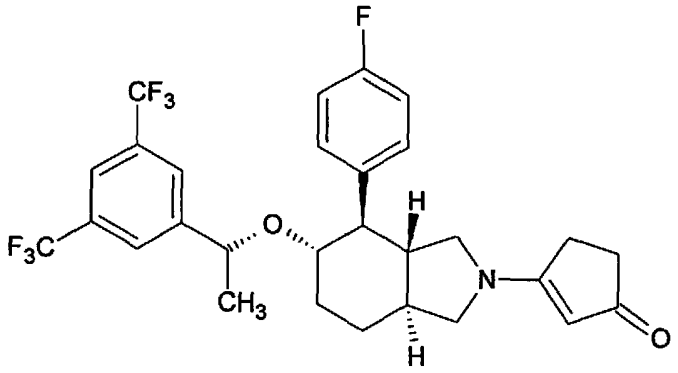
DETAILED DESCRIPTION OF THE INVENTION

[0020] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this application belongs. It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise.

[0021] Reference will now be made in detail to certain preferred methods of treatment, compounds and methods of administering these compounds. The invention is not limited to those preferred compounds and methods, but rather is defined by the claim(s) issuing herefrom.

Introduction

[0022] Serlopitant is a neurokinin-1 (NK-1) receptor antagonist. The present invention provides a method for treating chronic pruritus and related conditions using serlopitant or a pharmaceutically acceptable salt or hydrate thereof. Chemically, the generic name serlopitant refers to the compound of Compound 1:



Compound 1

The I.U.P.A.C. name for the compound is 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-4-(4-fluorophenyl)-1,3,3a,4,5,6,7,7a-octahydroisoindol-2-yl]cyclopent-2-en-1-one. Alternatively, Compound 1 may be named 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-2H-isoindol-2-yl]cyclopent-2-en-1-one. For purposes of the present invention, it is understood that any of these designations for Compound 1 may be interchangeably used and have the same meaning. It is further understood that the invention also encompasses the racemic form of serlopitant (Compound 1).

[0023] Serlopitant has previously been disclosed as a neurokinin-1 (NK-1) receptor antagonist, an inhibitor of tachykinin and, in particular, of substance P (J. Jiang, *et al.*, *J. Med. Chem.*, 2009, **52**:3039–3046)). Neurokinin receptors are part of the larger family of G-protein coupled receptors that elicit

many of their effects via activation of the inositol phosphate signal transduction pathway. NK-1 receptors are present in both the central and peripheral nervous system and in vascular endothelial cells, muscle and cells of the immune system. Compound 1 is unusually selective (>39,000 fold) for the cloned human NK-1 receptor over the cloned human NK-2 and NK-3 receptors, as demonstrated using Chinese hamster ovary cells stably expressing the respective receptors (Jiang *et al.*,2009). Jiang *et al.* showed that serlopitant binds to the human NK-1 receptor with a K_d of 46 pM and that it displaces substance P binding at the same receptor with an IC_{50} of 61 pM.

[0024] Compound 1 is a weak reversible inhibitor of human CYP-3A4, 2C8, 2C9, 2C19, 2D6, and 1A2 enzymes, the IC_{50} values of which are 39, 58, 30, 29, 35, and >100 μM, respectively. Serlopitant did not significantly induce CYP-3A4 mRNA in three individual preparations of human hepatocytes. These data suggest that serlopitant will have minimal drug-drug interaction liability in humans and that any drug-drug interactions will be reduced in comparison with other NK-1 receptor antagonists. Although broad-based counter-screening of serlopitant in more than 145 assays identified a number of weak activities between 1 and 10 μM, no assays for which IC_{50} <1 μM were observed. Therefore, off-target activities were more than 20000-fold less potent than hNK-1 activity (Jiang *et al.*, 2009).

[0025] It has been suggested serlopitant and its analogs would be useful in the prevention and treatment of a variety of clinical conditions characterized by the presence of an excess of tachykinin, in particular substance P, activity. Serlopitant has been disclosed as a treatment for emesis and for urinary incontinence (U.S. Patent Nos. US 7,217,731, US 7,345,083, US 7,544,815, US 7,645,790, and US 7,893,091, the disclosures of which are herein incorporated by reference; U.S. Published Application Nos. US 2009/0270477, US 2010/0113469, and US 2010/0209496, the disclosures of which are herein incorporated by reference; and PCT Publication WO 2007/146224, the disclosure of which is herein incorporated by reference).

[0026] The safety and tolerability of serlopitant have been evaluated in several human clinical trials for the treatment or prevention of with overactive bladder (OAB). In one investigation, a total of 557 patients with OAB were randomized into this double-blind, placebo-controlled and active- controlled (tolterodine), dose-ranging study. Serlopitant at 0.25 and 4 mg daily significantly reduced the number of daily micturitions compared with placebo. There were no drug-related serious adverse experiences and the drug was generally well tolerated. However, serlopitant did not show a dose response relationship with micturition frequency, and did not significantly influence the secondary efficacy end points of urinary urgency, urge incontinence and total incontinence. Tolterodine was numerically more effective than serlopitant at all efficacy end points and statistically significantly more effective than placebo. Serlopitant was not associated with the adverse experience of dry mouth common in patients receiving tolterodine, a muscarinic antagonist. (*See*: Frenkl, T. L. *et al.*, *J. Urology*, 2009, **181(4)**,

Suppl. S, p. 676; Frenkl, T. L. *et al.*, *Neurourol. Urodyn.*, 2009, **28**(2):143-144; Frenkl, T. L. *et al.*, *European Urology Supplements*, 2009, **8**(4):134; Frenkl, Tara L, *et al.*, *J. Urology*, 2010, **184**(2):616-622.)

Chemical Description of Serlopitant

[0027] The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylamino-ethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, ethanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of the present invention are meant to also include the pharmaceutically acceptable salts.

[0028] The term "solvate" refers to an aggregate that consists of a solute ion or molecule with one or more solvent molecules. "Solvates" include hydrates, that is, aggregates of a compound of interest with water. It will be understood that, as used herein, references to the compounds of the present invention are meant to also include the solvates.

[0029] The term "polymorph" refers to a crystalline form of a compound that can crystallize in different forms. The invention also encompasses polymorphs of serlopitant. Examples of polymorphs of serlopitant include without limitation anhydrous crystalline Forms I and II of free base serlopitant as

disclosed in US Pat. App. Pub. No. 2009/0270477 to Kuethe et al. Form I is characterized by diffraction peaks obtained from X-ray powder diffraction pattern corresponding to d-spacings of 10.4, 9.9, 9.2, 5.5, 5.0, 4.1, 3.9, 3.6 and 3.5 angstroms. Form II is characterized by diffraction peaks obtained from X-ray powder diffraction pattern corresponding to d-spacings of 7.7, 5.3, 4.9, 4.8, 4.6, 4.2, 3.9, 3.8 and 2.8 angstroms. US 2009/0270477 is incorporated herein by reference in its entirety.

[0030] Chemical Synthesis. Serlopitant may be prepared as described by Jiang *et al.* (*J. Med. Chem.* 2009, **52**:3039–3046), which is herein incorporated by reference in its entirety. Alternatively, the method of Kuethe *et al.*, as described in U.S. Patent No. 7,544,815, or Bunda *et al.*, as described in U.S. Patent No. 7,217,731, both of which are herein incorporated by reference in their entirety, may be used.

[0031] The method of Kuethe *et al.* is depicted in Figure 1. Briefly, commercially available 4-fluorophenylacetic acid (**2**) (Sigma-Aldrich Co. LLC, St. Louis, MO) is reacted with thionyl chloride in DMF/toluene to yield acid chloride (**3**). The acid chloride (**3**) is then reacted with the hydrochloride salt of the Weinreb amine ($CH_3NHOCH_3 \cdot HCl$) in the presence of sodium hydroxide to give 2-(4-fluorophenyl)-N-methoxy-N-methylacetamide (**4**). A vinyl Grignard reaction converts (**4**) to 1-(4-fluorophenyl)but-3-en-2-one (**5**). TES dienyl ether (**6**) is produced from the reaction of (**5**) with chlorotriethylsilane (TESCl) in the presence of iPr_2NEt_2.

[0032] Commercially available fumaryl chloride and two equivalents of (-)-menthol (both Sigma-Aldrich) are reacted to yield di-(-)-menthylfumarate (**7**). A Diels-Alder reaction between (**6**) and (**7**) produces (**8**). Any E-isomer of the diene (<5%) that is present does not react in the Diels-Alder reaction. Deprotection and epimerization of (**8**) in acid gives (**9**). The desilylation of (**8**) initially gave a mixture of 2,3-cis- and 2,3-trans-ketones, which, driven by crystallization of desired (**9**), isomerized to the predominantly trans compound. Reduction of (**9**) with lithium tri-*t*-butoxy aluminum hydride ($Li(t\text{-}BuO)_3AlH$), followed by lithium aluminum hydride ($LiAlH_4$), produces triol (**10**), which is then protected with n-propyl sulfonyl chloride ($nPrSO_2Cl_2$) to give (**11**).

[0033] *S*-BTBA ((*S*)-1-[3,5-bis(trifluoromethyl)] phenylethanol)) (**12**) is reacted with trichloroacetonitrile (Sigma-Aldrich) in the presence of base 1,8-diazabicycloundec-7-ene (DBU) to produce imidate (**13**). HBF_4 is used to catalyze the reaction of (**11**) with (**13**) to yield ether (**14**). Treatment with allylamine and bis-propylsulfonate cyclizes (**14**) to allylamine-protected pyrrolidine (**15**). Removal of the allyl protecting group with thiosalicylic acid and 1,4-bis(diphenylphosphino)butane (dppb), followed by bis(dibenzylideneacetone)palladium ($Pd_2(dba)_3$) and isolation with acetic acid gives crystalline (**16**). Finally, (**16**) is reacted with 1,3-cyclopentanedione (Sigma-Aldrich) in isopropyl alcohol to give

Compound 1. Compound 1 is a white to off-white powder. It is freely soluble in methanol, soluble in ethanol, slightly soluble in isopropyl acetate, sparingly soluble in isopropyl alcohol, ethyl acetate, and acetonitrile, and insoluble in water.

Pharmaceutical Compositions

[0034] Compositions containing serlopitant or a pharmaceutically acceptable salt, solvate or polymorph thereof as the active ingredient may be advantageously used to treat chronic pruritus. While it is possible for serlopitant or a pharmaceutically acceptable salt, solvate or polymorph thereof to be administered alone, it is preferable to present it as a formulation. The compositions, or dosage forms, may be administered or applied singly, or in combination with other agents. The formulations may also deliver serlopitant to a patient in combination with another pharmaceutically active agent.

[0035] The term "composition" as used herein is intended to encompass a product comprising specified ingredients in predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional pharmaceutically acceptable carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. Said compositions are prepared according to conventional mixing, granulating, or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

[0036] By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

[0037] Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, cornstarch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. A tablet may be made by compressing or molding the active ingredient optionally with one or more pharmaceutically acceptable ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active, or dispensing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered active ingredient and a suitable carrier moistened with an inert liquid diluent.

[0038] Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. In particular, a pharmaceutical composition of the present invention may comprise a liquid-filled capsule dosage form in which the active ingredient is in solution in certain combinations of liquid and semi-solid excipients. In one embodiment, the invention is directed to a solution comprising the active agent 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)-octahydro-2H-isoindol-2-yl]cyclopent-2-en-1-one (Compound 1) or a pharmaceutically acceptable salt, solvate or polymorph thereof, and an amphiphilic agent, said amphiphilic agent being a fatty acid ester of glycerol, propylene glycol or sorbitol, as described in U.S. Published Application No. 2010/0209496 (Dakou *et al.*), which is herein incorporated by reference in its entirety. Preferably, the amphiphilic agent consists essentially of mono- and di-glycerides of C8 to C12 saturated fatty acids and mixtures thereof.

[0039] Compositions for oral administration may also be formulated as aqueous suspensions containing the active ingredient in admixture with excipients suitable for the manufacture of aqueous suspensions. Oily suspensions may be formulated by suspending the active ingredient in a suitable oil. Oil-in-water emulsions may also be employed. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives.

[0040] The active ingredient of the present invention may be administered in an oral sustained release formulation. "Sustained release" refers to release of an active agent from a dosage form at a rate effective to achieve a therapeutic amount of the agent, or active metabolite thereof, in the systemic blood circulation over a prolonged period of time relative to that achieved by oral administration of a conventional formulation of the agent. Release of the agent occurs over an extended period of hours, for example, over a period of at least 6 hours, over a period of at least 8 hours, over a period of at least 12 hours, or over a period of at least 24 hours.

[0041] Suitable topical formulations and dosage forms include ointments, creams, gels, lotions, pastes, and the like, as described in *Remington: The Science and Practice of Pharmacy* (21st Edition, University of the Sciences in Philadelphia, 2005). Ointments are semi-solid preparations that are typically based on petrolatum or other petroleum derivatives. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery, and, preferably, will provide for other desired characteristics as well, e.g., emolliency or the like. Creams are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules (polymers) distributed substantially uniformly throughout the carrier liquid, which is typically aqueous, but also, preferably, contain an alcohol such as ethanol or isopropanol and, optionally, an oil. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing or stirring, or combinations thereof. Lotions are preparations to be applied to the skin surface without friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of finely divided solids and will typically contain suspending agents to produce better dispersions as well as compounds useful for localizing and holding the active agent in contact with the skin. Pastes are semisolid dosage forms in which the active agent is suspended in a suitable base. Depending on the nature of the base, pastes are divided between fatty pastes or those made from single-phase aqueous gels.

[0042] Various additives, known to those skilled in the art, may be included in the topical formulations. For example, solvents, including relatively small amounts of alcohol, may be used to solubilize certain drug substances. Other optional additives include opacifiers, antioxidants, fragrance, colorant, gelling

agents, thickening agents, stabilizers, surfactants and the like. Other agents may also be added, such as antimicrobial agents, to prevent spoilage upon storage, i.e., to inhibit growth of microbes such as yeasts and molds. For those drugs having an unusually low rate of permeation through the skin or mucosal tissue, it may be desirable to include a permeation enhancer in the formulation. The formulation may also contain irritation-mitigating additives to minimize or eliminate the possibility of skin irritation or skin damage resulting from the drug, the enhancer, or other components of the dosage form. The formulations may also contain ether physiologically acceptable excipients or other minor additives, such as fragrances, dyes, emulsifiers, buffers, cooling agents (e.g. menthol), antibiotics, stabilizers or the like. In some instances, one component may serve more than one function.

[0043] The concentration of the active agent in a topical formulation can vary a great deal, and will depend on a variety of factors, including the disease or condition to be treated, the nature and activity of the active agent, the desired effect, possible adverse reactions, the ability and speed of the active agent to reach its intended target, and other factors within the particular knowledge of the patient and physician. The formulations will typically contain on the order of about 0.1 wt % to 50 wt % active agent, preferably about 0.1 wt % to 5 wt % active agent, optimally about 5 wt % to 20 wt % active agent.

[0044] In some embodiments, a topical dosage form of serlopitant is formulated as a buccal or sublingual tablet or pill. Advantages of a buccal or sublingual tablet or pill include avoidance of first-pass metabolism and circumvention of gastrointestinal absorption. In addition to a therapeutically effective amount of serlopitant, the buccal or sublingual tablet or pill can contain suitable excipients, including without limitation any combination of fillers and diluents (e.g., mannitol and sorbitol), binding agents (e.g., sodium carbonate), wetting agents (e.g., sodium carbonate), disintegrants (e.g., crospovidone and croscarmellose sodium), lubricants (e.g., silicon dioxide [including colloidal silicon dioxide] and sodium stearyl fumarate), stabilizers (e.g., sodium bicarbonate), flavoring agents (e.g., spearmint flavor), sweetening agents (e.g., sucralose), and coloring agents (e.g., yellow iron oxide). The buccal or sublingual tablet or pill containing serlopitant can be used to treat, e.g., any pruritus-associated condition described herein.

[0045] The pharmaceutical compositions of the present invention may be formulated as a depot formulation for administration via intramuscular or subcutaneous injection. Depot formulations are efficient, well-tolerated, sustained or delayed release compositions of the active ingredient that are therapeutically effective for a number of weeks, such as at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks, or at least six weeks or more. In addition to the active agent, additional ingredients may be used in the depot formulations of the present invention

including surfactants, solubilizers, emulsifiers, preservatives, isotonicity agents, dispersing agents, wetting agents, fillers, solvents, buffers, stabilizers, lubricants, and thickening agents. A combination of additional ingredients may also be used. The amount of the active ingredient in a depot formulation will depend upon the severity of the pruritus being treated.

[0046] The compositions of the present invention may be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. The term "unit dosage form" is taken to mean a single dose wherein all active and inactive ingredients are combined in a suitable system, such that the patient or person administering the drug to the patient can open a single container or package with the entire dose contained therein, and does not have to mix any components together from two or more containers or packages. Typical examples of unit dosage forms are tablets or capsules for oral administration. These examples of unit dosage forms is not intended to be limiting in any way, but merely to represent typical examples in the pharmacy arts of unit dosage forms.

[0047] The compositions of the present invention may also be presented as a kit, whereby two or more components, which may be active or inactive ingredients, carriers, diluents, and the like, are provided with instructions for preparation of the actual dosage form by the patient or person administering the drug to the patient. Such kits may be provided with all necessary materials and ingredients contained therein, or they may contain instructions for using or making materials or components that must be obtained independently by the patient or person administering the drug to the patient.

Topical Compositions Comprising Serlopitant

[0048] Topical formulations for application to the skin or mucosa can be useful for treatment of conditions of the upper skin or mucosal layers and for transdermal or transmucosal administration of an active agent to the local tissue underlying the skin or mucosa and, if desired, into the blood for systemic distribution. Advantages of topical administration can include avoidance of first-pass metabolism, circumvention of gastrointestinal absorption, delivery of an active agent with a relatively short biological half-life, more controlled release of the active agent, administration of a more uniform plasma dosing of the active agent, and improvement in user compliance.

[0049] In general and in addition to the disclosure on topical formulations described elsewhere herein, compositions suitable for topical administration include without limitation liquid or semi-liquid preparations such as sprays, gels, liniments, lotions, oil-in-water or water-in-oil emulsions such as creams, foams, ointments and pastes, and solutions or suspensions such as drops (e.g., eye drops, nose drops and ear drops). In some embodiments, a topical composition comprises an active agent dissolved, dispersed or suspended in a carrier. The carrier can be in the form of, e.g., a solution, a

suspension, an emulsion, an ointment or a gel base, and can contain, e.g., petrolatum, lanolin, a wax (e.g., bee wax), mineral oil, a long-chain alcohol, polyethylene glycol or polypropylene glycol, a diluent (e.g., water and/or an alcohol [e.g., ethanol or propylene glycol]), an emulsifier, a stabilizer or a thickening agent, or a combination thereof. A topical composition can include, or a topical formulation can be administered by means of, e.g., a transdermal patch, a microneedle patch or an iontophoresis device. A transdermal patch can contain, e.g., a microporous membrane made of a suitable material (e.g., cellulose nitrate or acetate, propylene or a polycarbonate), a skin adhesive and backing material. A topical composition can deliver the active agent transdermally (including percutaneously and transmucosally) via a concentration gradient or an active mechanism (e.g., ionospheres).

[0050] Representative kinds of topical compositions are described below for purposes of illustration.

I. Topical Compositions Comprising a Permeation Enhancer

[0051] In some embodiments, a topical composition comprises serlopitant and a permeation enhancer. The composition can optionally contain an additional therapeutic agent. In certain embodiments, the composition contains serlopitant in free base form.

[0052] The permeation enhancer increases the permeability of the skin or mucosa to the therapeutic agent(s). In certain embodiments, the permeation enhancer is N-lauroyl sarcosine, sodium octyl sulfate, methyl laurate, isopropyl myristate, oleic acid, glyceryl oleate or sodium lauryl sulfoacetate, or a combination thereof. In certain embodiments, the composition contains on a weight/volume (w/v) basis the permeation enhancer in an amount of about 1-20%, 1-15%, 1-10% or 1-5%. To enhance further the ability of the therapeutic agent(s) to penetrate the skin or mucosa, the composition can also contain a surfactant, an azone-like compound, an alcohol, a fatty acid or ester, or an aliphatic thiol.

[0053] The composition can further contain one or more additional excipients. Suitable excipients include without limitation solubilizers (e.g., C_2-C_8 alcohols), moisturizers or humectants (e.g., glycerol [glycerin], propylene glycol, amino acids and derivatives thereof, polyamino acids and derivatives thereof, and pyrrolidone carboxylic acids and salts and derivatives thereof), surfactants (e.g., sodium laureth sulfate and sorbitan monolaurate), emulsifiers (e.g., cetyl alcohol and stearyl alcohol), thickeners (e.g., methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol and acrylic polymers), and formulation bases or carriers (e.g., polyethylene glycol as an ointment base). As a non-limiting example, the base or carrier of the composition can contain ethanol, propylene glycol and polyethylene glycol (e.g., PEG 300), and optionally an aqueous liquid (e.g., isotonic phosphate-buffered saline).

[0054] The topical composition can have any suitable dosage form, such as a solution (e.g., eye drop, nose drop or ear drop), a suspension, an emulsion, a cream, a lotion, a gel, an ointment, a paste, a jelly, a foam, a shampoo, or a spray. In some embodiments, the composition is applied to the skin or mucosa covering a surface area of about 10-800 cm^2, 10-400 cm^2 or 10-200 cm^2. The composition can deliver the therapeutic agent(s) to the skin or mucosa or the underlying tissue. The composition can also be formulated for transdermal administration of the therapeutic agent(s) to the systemic circulation, e.g., as a transdermal patch or a microneedle patch.

II. Topical Compositions Comprising a Permeation Enhancer and a Volatile Liquid

[0055] In further embodiments, a topical composition comprises serlopitant, a permeation enhancer and a volatile liquid. The composition can optionally contain an additional therapeutic agent. In certain embodiments, the composition contains serlopitant in free base form.

[0056] The permeation enhancer increases the permeability of the skin or mucosa to the therapeutic agent(s). In some embodiments, the permeation enhancer is selected from the group consisting of C_8-C_{18} alkyl aminobenzoates (e.g., C_8-C_{18} alkyl p-aminobenzoates), C_8-C_{18} alkyl dimethylaminobenzoates (e.g., C_8-C_{18} alkyl p-dimethylaminobenzoates), C_8-C_{18} alkyl cinnamates, C_8-C_{18} alkyl methoxycinnamates (e.g., C_8-C_{18} alkyl p-methoxycinnamates), and C_8-C_{18} alkyl salicylates. In certain embodiments, the permeation enhancer is octyl salicylate, octyl p-dimethylaminobenzoate or octyl p-methoxycinnamate, or a combination thereof.

[0057] The volatile liquid can be any volatile, skin- or mucosa-tolerant solvent. In certain embodiments, the volatile liquid is a C_2-C_5 alcohol or an aqueous solution thereof, such as ethanol or isopropanol or an aqueous solution thereof. An aerosol propellant (e.g., dimethyl ether) can be considered as a volatile liquid. In some embodiments, the volatile liquid functions as a carrier or vehicle of the composition.

[0058] The composition can optionally contain a thickening agent. Non-limiting examples of thickening agents include cellulosic thickening agents (e.g., ethyl cellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose), povidone, polyacrylic acids/polyacrylates (e.g., Carbopol® polymers), Sepigel® (polyacrylamide/isoparaffin/laureth-7), and the Gantrez® series of polymethyl vinyl ether/maleic anhydride copolymers (e.g., butyl ester of PMV/MA copolymer Gantrez® A-425).

[0059] In some embodiments, the composition contains on a weight basis about 0.5-10%, 0.5-5% or 1-5% of serlopitant, about 1-20%, 1-15% or 1-10% of the permeation enhancer, and about 40-98%, 45-95%, 50-90% or 60-80% of the volatile liquid. In further embodiments, the composition optionally

contains on a weight basis about 1-40%, 1-30%, 1-20% or 5-20% water and/or about 0.1-15%, 0.5-10% or 1-5% of a thickening agent.

[0060] For purposes of illustration, in certain embodiments a topical spray composition contains about 0.5-5% w/v of serlopitant, about 2-10% w/v of octyl salicylate or octyl p-methyoxycinnamate, and about 95% aqueous ethanol as the carrier. In further embodiments, a topic gel composition comprises about 0.5-5% w/v of serlopitant, about 1-10% w/v of octyl salicylate or octyl p-methyoxycinnamate, about 0.5-5% w/v of a Carbopol® polyacrylic acid, and about 70% aqueous ethanol as the carrier, and optionally about 1-10% w/v of a basic solution (e.g., 0.1 N NaOH). In additional embodiments, a topical lotion composition contains about 0.5-5% w/v of serlopitant, about 1-10% w/v of octyl salicylate or octyl p-methyoxycinnamate, about 1-5% w/v of ethyl cellulose or hydroxypropyl cellulose, and about 90% aqueous ethanol as the carrier.

[0061] The composition can further comprise other excipients, such as a compounding agent (e.g., paraffin oil, silicone oil, a vegetable oil, or a fatty ester such as isopropyl myristate), a diluent, a co-solvent (e.g., acetone or a glycol ether such as diethylene glycol monoethyl ether), an emulsifier, a surfactant (e.g., an ethoxylated fatty alcohol, glycerol mono stearate or a phosphate ester), a stabiliser, an antioxidant or a preservative (e.g., a hydroxybenzoate ester), or a combination thereof. For example, a co-solvent and/or a surfactant can be used to maintain the therapeutic agent(s) in solution or suspension at the desired concentration.

[0062] The topical composition can have any suitable dosage form, such as a cream, a lotion, a gel, an ointment, a mousse, a spray or aerosol, or any transdermal device (e.g., a patch) that administers a drug by absorption through the skin or mucosa. In some embodiments, the topical composition is applied to the skin or mucosa covering a surface area of about 10-800 cm^2, 10-400 cm^2 or 10-200 cm^2.

III. Topical Compositions Comprising a Permeation Enhancer and Another Excipient

[0063] In yet further embodiments, a topical composition comprises serlopitant, a permeation enhancer, and at least one of a lipophilic solvent, a formulation base and a thickener. In some embodiments, the composition contains a lipophilic solvent and a formulation base, or the same substance can function as both a lipophilic solvent and a formulation base. In further embodiments, the composition contains a lipophilic solvent, a formulation base and a thickener. The composition can optionally comprise an additional therapeutic agent. In certain embodiments, the composition contains serlopitant in free base form.

[0064] The permeation enhancer increases the permeability of the skin or mucosa to the therapeutic agent(s). Non-limiting examples of permeation enhancers include dimethyl sulfoxide (DMSO),

decylmethylsulfoxide, laurocapram, pyrrolidones (e.g., 2-pyrrolidone and N-methyl-2-pyrrolidine), surfactants, alcohols (e.g., oleyl alcohol), polyethylene glycol (e.g., PEG 400), diethylene glycol monoethyl ether, oleic acid, and fatty acid esters (e.g., isopropyl myristate, methyl laurate, glycerol monooleate, and propylene glycol monooleate).

[0065] Non-limiting examples of liphophilic solvents include lipophilic alcohols (e.g., hexylene glycol, octyldodecanol, oleyl alcohol and stearyl alcohol), polyethylene glycol (e.g., PEG 100, PEG 300, PEG 400 and PEG 3350), diethylene glycol monoethyl ether, polysorbates (e.g., Tween® 20 to 80), Labrasol®, fatty acid esters (e.g., isopropyl myristate and diisopropyl adipate), diethyl sebacate, propylene glycol monocaprylate, propylene glycol laurate, mono- and di-glycerides (e.g., Capmul® MCM), medium-chain triglycerides, caprylic/capric triglyceride, glyceryl monocaprylate, glyceryl mono-oleate, glyceryl mono-linoleate, glycerol oleate/propylene glycol, mineral oil, and vegetable oils.

[0066] A liphophilic solvent may also function as a formulation base or carrier. For example, polyethylene glycol (e.g., from PEG 100 to PEG 3500, such as PEG 300, PEG 400 and PEG 3350) can function as a liphophilic solvent and a formulation base.

[0067] The composition can also contain a hydrophilic solvent, such as a C_1-C_5 alcohol (e.g., ethanol, isopropanol, glycerol, propylene glycol and 1,2-pentanediol) and/or water.

[0068] The composition can contain a thickener to increase the viscosity and/or the physical stability of the composition. Examples of thickeners include without limitation glycerol, stearyl alcohol, and polymers (e.g., polydimethylsiloxane [dimethicone] and Carbopol® polymers).

[0069] In some embodiments, the composition further contains an antioxidant. Non-limiting examples of antioxidants include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), tocopherols (e.g., Vitamin E and esters thereof), flavinoids, glutathione, ascorbic acid and esters thereof, DMSO, and chelating agents (e.g., EDTA and citric acid).

[0070] In certain embodiments, the topical composition comprises on a w/w basis about 0.5-10% or 1-5% of serlopitant, about 2-30% or 5-20% of a permeation enhancer, about 20-80% or 30-70% of a lipophilic solvent that may also function as a formulation base, about 0.1-10% or 1-7.5% of a thickener, and about 0.01-2% or 0.05-1% of an antioxidant. As a non-limiting example, a topical composition can contain serlopitant, PEG 400 and/or PEG 3350 as lipophilic solvent(s) and formulation base(s), diethylene glycol monoethyl ether, oleyl alcohol and/or isopropyl myristate as permeation enhancer(s), stearyl alcohol as a thickener, and BHT as an antioxidant.

[0071] The topical composition can have any suitable dosage form, such as a cream, a lotion, a gel, an ointment, a jelly, a paste, or any transdermal device (e.g., a patch) that administers a drug by absorption through the skin or mucosa.

IV. Topical Compositions Comprising a Permeation Enhancer and an Adhesive

[0072] In additional embodiments, a topical composition comprises serlopitant, a permeation enhancer and an adhesive. The composition can optionally contain an additional therapeutic agent. In certain embodiments, the composition contains serlopitant in free base form.

[0073] The permeation enhancer increases the permeability of the skin or mucosa to the therapeutic agent(s). The permeation enhancer can be, e.g., a fatty acid ester having a fatty acyl chain length of C_8-C_{20} or C_{12}-C_{18} and a C_1-C_6 or C_2-C_4 alcohol component (e.g., isopropanol). In certain embodiments, the permeation enhancer is isopropyl myristate or isopropyl palmitate. In some embodiments, the permeation enhancer is in an amount of about 0.1-20%, 0.5-15%, 1-15%, 2-12% or 4-10% by weight of the composition or the skin-contacting layer of a transdermal patch.

[0074] The adhesive maintains contact of the topical composition to the skin or mucosa. Non-limiting examples of adhesives include acrylics/acrylates (e.g., polyacrylates, including polyalkyl acrylates and Duro-Tak® polyacrylates), polyvinyl acetate, ethylenevinylacetate copolymers, polysiloxanes, polyurethanes, plasticized polyether block amide copolymers, natural and synthetic rubbers, plasticized styrene-butadiene rubber block copolymers (e.g., Duro-Tak® 87-6173), and mixtures thereof.

[0075] The topical composition can comprise one or more additional excipients. The additional excipient(s) can be, e.g., a diluent, an emollient, a plasticizer, or an agent that reduces irritation to the skin or mucosa, or a combination thereof.

[0076] In certain embodiments, the topical composition prior to application to the skin or mucosa is substantially free of water, tetraglycol (glycofurol) and/or a hydrophilic organic solvent (e.g., a C_1-C_5 alcohol).

[0077] The composition can administer the therapeutic agent(s) transdermally (including percutaneously and transmucosally) through a body surface or membrane such as intact unbroken skin or intact unbroken mucosal tissue into the systemic circulation.

[0078] In some embodiments, the topical composition is in the form of a transdermal patch for application to the skin or mucosa. The patch has a skin- or mucosa-contacting layer ("skin-contacting layer" for simplicity) laminated or otherwise attached to a support layer. The skin-contacting layer can

be covered by a removable release liner before use to protect the skin-contacting surface and to keep it clean until it is applied to the skin or mucosa.

[0079] The support layer of the patch acts as a support for the skin-contacting layer and as a barrier that prevents loss of the therapeutic agent(s) in the skin-contacting layer to the environment. The material of the support layer is compatible with the therapeutic agent(s), the permeation enhancer and the adhesive, and is minimally permeable to the components of the patch. The support layer can be opaque to protect the components of the patch from degradation via exposure to ultraviolet light. The support layer is also capable of binding to and supporting the adhesive layer, yet is sufficiently pliable to accommodate the movements of the subject using the patch. The material of the support layer can be, e.g., a metal foil, a metalized polyfoil, or a composite foil or film containing a polymer (e.g., a polyester [such as polyester terephthalate] or aluminized polyester, polyethylene, polypropylene, polytetrafluoroethylene, a polyethylene methyl methacrylate block copolymer, a polyether block amide copolymer, a polyurethane, polyvinylidene chloride, nylon, a silicone elastomer, rubber-based polyisobutylene, styrene, or a styrene-butadiene or styrene-isoprene copolymer). The release liner can be made of the same material as the support layer, or can be a film coated with an appropriate release surface.

Pruritus

[0080] Pruritus is a physiological perception within the sensory neuronal network in the skin which, along with pain and physical or mechanical stimuli, can serve as a warning system against potential bodily threats. Itching is an unpleasant sensation that can lead to scratching, but is independent of pain. The International Federation for the Study of Itch (IFSI) defines chronic pruritus (as opposed to acute pruritus) as itching that lasting six weeks or longer (S. Ständer *et al.*, *Acta Derm. Venereol.*, 2007, **87**(4):291–4). Several factors in and on the skin can activate the sensory nerve fibers or modulate their activity and thus trigger, suppress, or exacerbate itching. Physical stimuli such as cold and heat modulate the perception of itching; painful heat and cold can significantly diminish it, while moderate cold intensifies it (Valet et al., *J. Invest. Dermatol.*, 2008, **128**(2):426–33.). Mechanical factors such as rubbing or scratching the skin can briefly suppress itching by activating nerve fibers that selectively activate and de-activate certain areas of the brain (Yosipovitch et al., *J. Invest. Dermatol.*, 2008, **128**(7):1806–11).

[0081] Chronic pruritus can seriously diminish the quality of life in its sufferers as it can be intractable and incapacitating. It is a seriously debilitating condition, comparable to chronic pain, which can lead to frustration, desperation and depression. Moreover, chronic scratching often produces open skin

lesions, subject to primary or secondary infection, scarring and potential disfigurement. Chronic pruritus is often an indication of underlying disease and is always present in diseases such as urticaria and atopic dermatitis. Diagnosis of the underlying disease is desirable and clinical presentation, patient history, and patient self-evaluation form important parts of such diagnosis.

[0082] According to Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) (Association of the Scientific Medical Societies of Germany) guidelines, diseases and disorders with chronic pruritus as a symptom may be classified by whether the skin is inflamed or not inflamed (S. Ständer, *Clin. Exp. Dermatol.*, 2006, **31**(6):762–7). The IFSI further characterizes pruritus as dermatologic, systemic, neurogenic, psychogenic, mixed and other. Chronic pruritus on non-inflamed skin may result from dermatological diseases, including atopic diathesis, asteatosis, porphyria, suburticarial stages of solar injury, cholinergic, adrenergic urticaria, initial stage of mastocytosis, bullous pemphigoid, and Duhring's disease (dermatitis herpetiformis); from endocrine and metabolic disorders, such as chronic renal insufficiency and the dialysis needed treat it, hepatopathies with cholestasis, diabetes mellitus, malabsorption disorders, anorexia, gluten-enteropathies, hyperthyroidism, hypothyroidism, hyperparathyroidism, and perimenopausal pruritus; from infections including HIV infection, parasites, *Helicobacter pylori*, and helminth-related; from hemotological and lymphoproliferative diseases such as iron deficiency, polycythaemica vera, hypereosinophilia syndrome, myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, plasmocytoma, and systemic mastocytosis; from solid malignant tumors including cervical, breast, prostate or large intestinal cancer, and carcinoid tumors; from neurological disorders such as brachioradial pruritus, notalgia paraesthetica, post-zoster neuralgia, vulvodynia, neuropathies of various origin, multiple sclerosis, tumors, abscesses, underperfusion, infarctions involving the CNS/spinal cord; from psychogenic disorders such as depression, schizophrenia, and tactile hallucinations; and from intrahepatic cholestasis in pregnant women (pruritus gravidarum).

[0083] Chronic pruritus on inflamed skin may be observed in patients with inflammatory skin disease including, but not limited to, atopic dermatitis, allergic, irritant contact dermatitis, exsiccation dermatitis, nummular and dyshidrotic dermatitis, lichen planus, lichen sclerosus et atrophicus, polymorphous light eruption psoriasis, Grover's disease, mucinosis, mastocytosis, and urticaria; infectious skin diseases such as mycoses, bacterial and viral infections, scabies, pediculosis, insect bites, and folliculitides; autoimmune skin diseases including Bullous skin disorders, especially dermatitis herpetiformis (Duhring's disease), and bullous pemphigoid; genodermatoses such as Darier's disease, and Hailey-Hailey disease; pregnancy-related skin diseases including polymorphic eruption of pregnancy (PEP,

formerly known as PUPPP), atopic eruption of pregnancy, and pemphigoid gestationis; and neoplasias such as cutaneous T-cell lymphoma (especially the erythrodermic form).

[0084] Prurigo nodularis (PN), or nodular prurigo, is a particularly severe form of chronic itching that may treated by methods and compositions of the present invention. Characterized by itchy, excoriated, lichenified papules and nodules, PN can occur at any age, but most often presents in middle-aged and elderly patients on their arms and legs (E. Weisshaar and S. Ständer, *Acta Derm. Venereol.*, 2012, **92**:532-533). The etiology of PN is unknown, but it usually occurs in patients with a personal or family history of atopic dermatitis, and often with concomitant medical conditions such as hepatic or renal function, local trauma or insult to the skin, infection, and HIV or other immunodeficiencies. PN may result in permanent changes to the skin, including nodular lichenification, hyperkeratosis, hyperpigmentation, and skin thickening.

Combination Therapies with Serlopitant and Other Antipruritic Agents

[0085] Serlopitant, alone or in combination with one or more additional antipruritic agents, can be used to treat pruritus (including acute and chronic pruritus) associated with any condition. The itch sensation can originate, e.g., in the peripheral nervous system (e.g., dermal or neuropathic itch) or in the central nervous system (e.g., neuropathic, neurogenic or psychogenic itch).

[0086] Examples of pruritus-associated conditions include without limitation those described elsewhere herein and the following:

dermatological disorders and conditions (including inflammatory and non-inflammatory skin conditions), including but not limited to adult blaschkitis, amyloidoses (e.g., primary cutaneous amyloidosis [including macular amyloidosis, lichen amyloidosis and nodular amyloidosis]), burns (e.g., chemical burns and sunburn), dermatitis {e.g., atopic dermatitis, contact dermatitis (including allergic contact dermatitis, irritant contact dermatitis and photodermatitis), eczema (e.g., autosensitization dermatitis, dermatitis herpetiformis [Duhring's disease], discoid eczema, dyshidrosis [pompholyx], hand eczema, id reaction [generalized eczema], nummular eczema, stasis dermatitis [gravitational eczema], venous eczema and xerotic eczema), pustular dermatitis (e.g., eosinophilic pustular folliculitis [Ofuji's disease], reactive arthritis [Reiter's disease] and subcorneal pustular dermatosis [Sneddon-Wilkinson disease]), and seborrheic dermatitis (e.g., infantile seborrheic dermatitis, Leiner's disease and pityriasis simplex capillitii [dandruff])}, erythroderma (exfoliative dermatitis), folliculitis, pseudofolliculitis barbae (barber's itch), hidradenitis suppurativa, ichthyoses (e.g., ichthyosis vulgaris, congenital ichthyosis, epidermolytic hyperkeratosis and lamellar ichthyosis), lichen planus (e.g., cutaneous lichen planus and oral lichen planus), lichen sclerosis (e.g., lichen sclerosis et atrophicus of the vulva), lichen simplex

(e.g., lichen simplex chronicus [neurodermatitis]), linear IgA bullous dermatosis (linear IgA dermatosis), lupus erythematosus (e.g., cutaneous lupus erythematosus, discoid lupus erythematosus and systemic lupus erythematosus), miliaria (sweat rash), palmoplantar keratoderma (e.g., punctate palmoplantar keratoderma), pityriasis (e.g., pityriasis amiantacea, pityriasis lichenoides [including pityriasis lichenoides chronica and pityriasis lichenoides et varioliformis acuta], pityriasis rosea, pityriasis rubra pilaris [Devergie's disease] and pityriasis versicolor), prurigo (e.g., actinic prurigo, Besnier's prurigo, prurigo nodularis, prurigo pigmentosa and prurigo simplex), pruritus ani, pruritus scroti, pruritus vulvae, psoriasis (e.g., erythrodermic psoriasis, Guttate psoriasis [eruptive psoriasis], psoriasis vulgaris [chronic stationary psoriasis], pustular psoriasis, and pustulosis palmaris et plantaris), parapsoriasis (e.g., large plaque parapsoriasis and small plaque parapsoriasis [chronic superficial dermatitis]), puncta pruritica (itchy points), rashes (e.g., intertrigo and perioral dermatitis), rosacea, urticaria (e.g., contact urticaria [including hives] and idiopathic urticaria), vitiligo, xerosis (dry skin), chapped skin (e.g., chapped feet), scalp pruritus, scab healing, scar development, and development of moles, pimples and ingrown hair;

medical disorders and conditions (including peripheral and systemic disorders), including but not limited to atopic diathesis, autoimmune disorders (e.g., celiac disease, dermatomyositis, Graves' disease, pemphigoid [e.g., bullous pemphigoid], scleroderma and Sj□gren's syndrome), blood disorders (e.g., anemia [e.g., iron deficiency anemia and sickle cell anemia], hypercalcemia, myelodysplastic syndromes and polycythemia [e.g., polycythemia vera]), Creutzfeldt-Jakob disease (e.g., prion pruritus), diabetes mellitus, genetic diseases (e.g., Alagille syndrome, Darier's disease, epidermolysis bullosa, Hailey-Hailey disease and Sj□gren-Larsson syndrome), Grover's disease, HIV/AIDS, kidney disorders (e.g., diabetic nephropathy, glomerulonephritis, chronic kidney disease, end-stage kidney disease and chronic kidney failure), uraemia (e.g., uremic pruritus [renal pruritus]), liver diseases (e.g., cirrhosis [e.g., primary biliary cirrhosis], hepatitis [including hepatitis A, B, C, D and E and their chronic conditions], and liver failure), cholestasis (e.g., cholestatic pruritus), jaundice (e.g., biliary pruritus), lymphadenopathy (e.g., enlarged lymph nodes), mast cell diseases (e.g., mast cell activation syndrome and mastocytosis), multiple sclerosis, neuropathies (e.g., peripheral neuropathy [e.g., brachioradial pruritus, notalgia paresthetica, polyneuropathy and small fiber peripheral neuropathy]), nerve irritation, pinched nerves, parathyroid disorders (e.g., hyperparathyroidism and hypoparathyroidism), thyroid disorders (e.g., hyperthyroidism, hypothyroidism and myxedema), stroke, cancers {e.g., carcinoid syndrome, leukemia (e.g., leukemia cutis and lymphatic leukemia), lymphomas (e.g., Hodgkin's disease and non-Hodgkin lymphomas [e.g., cutaneous B-cell lymphoma and cutaneous T-cell lymphoma (including mycosis fungoides and Sézary's disease)]), Kaposi's sarcoma, multiple myeloma and skin cancers}, tumors (e.g., brain tumor, plasmacytoma, and solid tumors of the cervix, colon and prostate), paraneoplastic pruritus, psychiatric disorders (e.g., stress, anxiety

disorders, delusional parasitosis, depression, obsessive-compulsive disorders [e.g., neurotic excoriation], and tactile hallucinations), aging (e.g., senile pruritus) and changes in hormonal balances associated with aging (e.g., perimenopause and menopause);

infections and infestations, including but not limited to cercarial dermatitis (swimmer's itch), insect bites and stings (e.g., by ants, bees, chiggers, fleas, lice [including body lice, head lice and pubic lice], mites, mosquitos, spiders, ticks and wasps), scabies, bacterial infections (e.g., abscess, dermatitis gangrenosa, ecthyma, erythrasma, impetigo and Lyme disease), fungal infections (e.g., candidiasis, dermatophytosis, tinea corporis [ringworm of the body], tinea cruris [jock itch] and tinea pedis [athlete's foot]), viral infections {e.g., herpes (including herpes zoster [shingles] and post-herpetic itch), measles, parvovirus infections (e.g., parvovirus B19), varicella (chickenpox) and Yellow fever}, and worm infections {e.g., helminths (e.g., helminthiasis [helminthosis]), hookworms (e.g., cutaneous larva migrans), *Onchocerca* worms (e.g., onchocerciasis [river blindness]), pinworms, roundworms (e.g., filariasis and trichinosis) and *Schistosoma* worms (e.g., schistosomiasis)};

reactions to allergens and irritants, including but not limited to allergic rhinitis (e.g., pollinosis [including hay fever]), asthma, animal allergens (e.g., cat dander and dog dander), chemical allergens (e.g., acids [e.g., abietic acid and sorbic acid], cosmetics, detergents, dyes, fabric softeners, fungicides, hydroxyethyl starch and latex), food allergens (e.g., milk proteins, peanuts, tree nuts, seafood, spices, preservatives [e.g., nitrates], vitamins [e.g., vitamins A and B], alcohol, caffeine and monosodium glutamate), metal and metal salt allergens (e.g., chromium, cobalt, gold and nickel and salts thereof), plant allergens (e.g., Balsam of Peru and urushiol [e.g., in poison ivy, poison oak and poison sumac]), chemical irritants (e.g., acids, alkalis, metalworking fluids, solvents, surfactants, detergents, soaps, cleaning products, cosmetics, perfumes, deodorants, antiperspirants, food flavorings, spices, preservatives [e.g., formaldehyde and parabens], monomers and polymers [e.g., acrylics, epoxy resins, ethylene oxide, latex and lacquers], and oils [e.g., kerosene]), fabrics (e.g., wool), plant irritants (e.g., alkyl resorcinols [e.g., in *Grevillea banksii*, *Grevillea "Robyn Gordon"* and *Gingko biloba*]), and physical irritants (e.g., water [e.g., aquadynia and aquagenic pruritus), low humidity from air conditioning, and cold temperature);

pruritus caused by drugs/medication, including but not limited to chloroquine, hydroxyethyl cellulose, hydroxyethyl starch, angiotensin-converting enzyme inhibitors, xanthine oxidase inhibitors (e.g., allopurinol), antibiotics (e.g., isoniazid, neomycin, penicillin, sulfonamides and vancomycin), antifungals (e.g., fluconazole, griseofulvin, itraconazole and ketoconazole), neuroleptics/antipsychotics (e.g., phenothiazines), antiarrhythmic drugs (e.g., amiodarone and quinidine), chemotherapeutic drugs, diuretic drugs (e.g., hydrochlorothiazide), statins (e.g., simvastatin), and drugs (e.g., opioids) that activate the histamine H_1 receptor or trigger histamine release; and

conditions related to pregnancy, including but not limited to gestational pemphigoid, impetigo herpetiformis, intrahepatic cholestasis of pregnancy (pruritus gravidarum), polymorphic eruption of pregnancy, prurigo of pregnancy, pruritic folliculitis of pregnancy, and pruritic urticarial papules and plaques of pregnancy.

[0087] One or more additional antipruritic agents can optionally be used in combination with serlopitant to treat pruritus (including acute and chronic pruritus). Examples of antipruritic agents include without limitation:

antihistamines, including but not limited to antihistamines that inhibit action at the histamine H_1 receptor (e.g., acrivastine, antazoline, azelastine, bilastine, brompheniramine, buclizine, bromodiphenhydramine, carbinoxamine, cetirizine, chlorpromazine, cyclizine, chlorpheniramine, chlorodiphenhydramine, clemastine, cyproheptadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, dimetindene, diphenhydramine, doxepin, doxylamine, ebastine, embramine, fexofenadine, hydroxyzine, levocetirizine, loratadine, meclozine, mepyramine, mirtazapine, olopatadine, orphenadrine, phenindamine, pheniramine, phenyltoloxamine, promethazine, pyrilamine, quetiapine, rupatadine, tripelennamine and triprolidine), and antihistamines that inhibit action at the histamine H_4 receptor (e.g., thioperamide, JNJ 7777120 and VUF-6002), and analogs and derivatives thereof;

serotonin receptor antagonists, including but not limited to 5-HT_2 antagonists (e.g., clozapine, cyproheptadine, ketanserin, pizotifen and quetiapine) and 5-HT_3 antagonists (e.g., alosetron, cilansetron, dolasetron, granisetron, ondansetron, palonosetron and tropisetron), and analogs and derivatives thereof;

neurokinin-1 (NK-1) receptor antagonists, including but not limited to aprepitant, casopitant (GW679769), dapitant, ezlopitant, fosaprepitant, lanepitant (LY-303870), maropitant, netupitant, nolpitant, orvepitant, rolapitant, vestipitant, vofopitant, AV-818, BIIF 1149CL, CP122,721, DNK-333, GSK-424887, L-733060, L-759274, LY-686017, M516102 and TA-5538, and analogs and derivatives thereof;

opioid receptor antagonists, including but not limited to butorphanol, cyprodime, levallorphan (lorfan or naloxiphan), nalbuphine, nalorphine (lethidrone or nalline), naloxone, naloxol, nalmefene, naltrexone (e.g., naltrexone 1% cream) and naltrexol, and analogs and derivatives thereof;

opioid receptor agonists, including but not limited to selective kappa opioid receptor agonists (e.g., asimadoline, bremazocine, dynorphin, enadoline, ketazocine, nalfurafine, salvinorin A, 2-methoxymethyl salvinorin B, 2-ethoxymethyl salvinorin B, 2-fluoroethoxymethyl salvinorin B,

spiradoline, tifluadom, BRL-52537, FE 200665, GR-89696, HZ-2, ICI-199,441, ICI-204,448, LPK-26, U-50488 and U-69,593), and analogs and derivatives thereof;

Janus kinase (JAK) inhibitors, including but not limited to JAK1 inhibitors (e.g., GLPG0634 and GSK2586184), JAK2 inhibitors (e.g., lestaurtinib, pacritinib, CYT387 and TG101348), JAK1/JAK2 inhibitors (e.g., baricitinib and ruxolitinib), and JAK3 inhibitors (e.g., tofacitinib), and analogs and derivatives thereof;

immunomodulators and immunosuppressants, including but not limited to thalidomide, antimetabolites (e.g., antifolates such as methotrexate), and calcineurin inhibitors (e.g., ciclosporin [cyclosporin], pimecrolimus and tacrolimus), and analogs and derivatives thereof;

antidepressants, including but not limited to tricyclic antidepressants (e.g., amitriptyline, amitriptylinoxide, amoxapine, dosulepin [dothiepin], doxepin and melitracen), tetracyclic antidepressants (e.g., amoxapine, maprotiline, mazindol, mianserin, mirtazapine and setiptiline), selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), and serotonin-norepinephrine reuptake inhibitors (SNRIs, e.g., bicifadine, duloxetine, milnacipran, levomilnacipran, sibutramine, venlafaxine, desvenlafaxine and SEP-227162), and analogs and derivatives thereof;

anticonvulsants, including but not limited to carbamazepine, gabapentin, pregabalin, and valproic acid and salts thereof (e.g., sodium valproate), and analogs and derivatives thereof;

corticosteroids, including but not limited to hydrocortisone types (e.g., cortisone and derivatives thereof [e.g., cortisone acetate], hydrocortisone and derivatives thereof [e.g., hydrocortisone acetate, hydrocortisone-17-aceponate, hydrocortisone-17-buteprate, hydrocortisone-17-butyrate and hydrocortisone-17-valerate], prednisolone, methylprednisolone and derivatives thereof [e.g., methylprednisolone aceponate], prednisone, and tixocortol and derivatives thereof [e.g., tixocortol pivalate]), betamethasone types (e.g., betamethasone and derivatives thereof [e.g., betamethasone dipropionate, betamethasone sodium phosphate and betamethasone valerate], dexamethasone and derivatives thereof [e.g., dexamethasone sodium phosphate], and fluocortolone and derivatives thereof [e.g., fluocortolone caproate and fluocortolone pivalate]), halogenated steroids (e.g., alclometasone and derivatives thereof [e.g., alclometasone dipropionate], beclometasone and derivatives thereof [e.g., beclometasone dipropionate], clobetasol and derivatives thereof [e.g., clobetasol-17-propionate], clobetasone and derivatives thereof [e.g., clobetasone-17-butyrate], desoximetasone and derivatives thereof [e.g., desoximetasone acetate], diflorasone and derivatives thereof [e.g., diflorasone diacetate], diflucortolone and derivatives thereof [e.g., diflucortolone valerate], fluprednidene and derivatives thereof [e.g., fluprednidene acetate], fluticasone and derivatives thereof [e.g., fluticasone propionate], halobetasol [ulobetasol] and derivatives thereof [e.g., halobetasol proprionate], halometasone and

derivatives thereof [e.g., halometasone acetate], and mometasone and derivatives thereof [e.g., mometasone furoate]), acetonides and related substances (e.g., amcinonide, budesonide, ciclesonide, desonide, fluocinonide, fluocinolone acetonide, flurandrenolide [flurandrenolone or fludroxycortide], halcinonide, triamcinolone acetonide and triamcinolone alcohol), and carbonates (e.g., prednicarbate), and analogs and derivatives thereof;

local anesthetics, including but not limited to amides (e.g., articaine, bupivacaine, cinchocaine [dibucaine], etidocaine, levobupivacaine, lidocaine [e.g., lidocaine 2.5-5% cream], prilocaine [e.g., prilocaine 2.5% cream], EMLA [lidocaine 2.5%/prilocaine 2.5% cream], mepivacaine, ropivacaine and trimecaine), esters (e.g., benzocaine, chloroprocaine, cocaine, cyclomethycaine, dimethocaine [larocaine], piperocaine, procaine [novocaine], proparacaine, propoxycaine, stovaine and tetracaine [amethocaine]), ethers (e.g., polidocanol [e.g., polidocanol 3% foam] and pramocaine [pramoxine] [e.g., pramoxine 1% cream]), and naturally derived local anesthetics (e.g., cocaine, eugenol, menthol, saxitoxin, neosaxitoxin and tetrodotoxin), and analogs and derivatives thereof;

counterirritants and cooling agents, including but not limited to capsaicin, camphor, mint oil, menthol (e.g., menthol 1-3% cream), and phenol (e.g., in calamine lotion), and analogs and derivatives thereof;

moisturizers, including but not limited to aqueous moisturizers, low pH moisturizers containing an acid (e.g., lactic acid), and moisturizers containing a humectant that attracts and retains water (e.g., glycerol, sorbitol, lactate, urea, and hyaluronic acid and salts thereof), an occlusive that prevents evaporation {e.g., oils (e.g., mineral oil and silicone oil [e.g., dimethicone]) and petroleum jelly (petrolatum)}, and/or an emollient that provides partial hydration and occlusion (e.g., oils, waxes [e.g., lanolin and paraffin], lipids [e.g., phospholipids, ceramides, triglycerides, glycol stearate, glyceryl stearate, fatty acids and squalene], and sterols [e.g., cholesterol and phytosterol]), and analogs and derivatives thereof; and

other kinds of antipruritic agents, including but not limited to S-adenosyl methionine, botulinum toxin (e.g., botulinum toxin types A and B), vitamin D and analogs and derivatives thereof (e.g., calcitriol and calcipotriol [calcipotriene]), non-steroidal anti-inflammatory drugs (NSAIDs, e.g., aspirin), cannabinoid receptor agonists (e.g., CB_2 agonists, such as palmitoylethanolamide), inhibitors of cytokines (e.g., antibodies to interleukins, such as IL-31), antagonists of the prostaglandin D_2 receptor (DP_1) and/or the chemoattractant receptor homologous molecule expressed on TH_2 cells (CRTH2) (e.g., TS-022), phosphodiesterase (PDE) inhibitors (e.g., PDE4 inhibitors, such as apremilast), protease-activated receptor 2 (PAR2) antagonists (e.g., GB83), transient receptor potential vanilloid (TRPV) antagonists (e.g., TRPV1 antagonists, such as capsazepine and SB-705498), inhibitors of neurotrophic tyrosine kinase receptors (e.g., TrkA inhibitors, such as CT327), antimicrobials (including

antibiotics, antifungals, antivirals and antiparasitics, such as crotamiton and rifampin [rifampicin]), bile absorption-reducing or bile sequestering agents (e.g., ursodeoxycholic acid [ursodiol]), ultraviolet radiation (e.g., ultraviolet A and B), and therapeutic agents that treat the underlying causes of the pruritus-associated conditions, and analogs and derivatives thereof.

[0088] If desired (e.g., for relief from pruritus during the day), a non-sedating antipruritic agent can be used. For example, second-generation and third-generation antihistamines are designed to be non-sedating, or less sedating than first-generation antihistamines. Non-limiting examples of second-generation and third-generation antihistamines include acrivastine, astemizole, azelastine, bepotastine, bilastine, cetirizine, levocetirizine, ebastine, fexofenadine, ketotifen, levocabastine, loratadine, desloratadine, mizolastine, olopatadine, quifenadine, rupatadine and terfenadine.

[0089] In some embodiments, a corticosteroid of moderate or medium potency is used in combination with serlopitant to treat a pruritus-associated condition. Examples of corticosteroids having moderate or medium potency include Groups III, IV and V corticosteroids under the 7-group US classification system and Class II corticosteroids under the 4-class European classification system, including without limitation amcinonide 0.1% (e.g., cream), betamethasone dipropionate 0.05% (e.g., Diprosone® cream/ointment), betamethasone valerate 0.1% (e.g., cream/ointment), clobetasone butyrate 0.05% (e.g., Eumovate® cream), desonide 0.05% (e.g., Tridesilon® cream/ointment and DesOwen® cream/ointment), fluocinolone acetonide 0.01-0.2% (e.g., Synalar® cream/ointment and Synemol® cream), flurandrenolide 0.05% (e.g., Cordran® tape), fluticasone propionate 0.005% (e.g., Cutivate® ointment), fluticasone propionate 0.05% (e.g., Cutivate® cream), halometasone 0.05% (e.g., cream), hydrocortisone butyrate 0.1% (e.g., Locoid® cream/ointment), hydrocortisone valerate 0.2% (e.g., Westcort® cream/ointment), mometasone furoate 0.1% (e.g., Elocon® cream/ointment), triamcinolone acetonide 0.025-0.5% (e.g., Aristocort® cream/ointment, Kenacomb® cream/ointment, Kenalog® cream and Viaderm® KC cream/ointment), and triamcinolone diacetate 0.5% (e.g., cream/ointment).

[0090] The optional additional antipruritic agent(s) can be administered to a subject suffering from pruritus concurrently with (e.g., in the same composition as serlopitant or in separate compositions) or sequentially to (before or after) administration of serlopitant. Serlopitant and the optional additional antipruritic agent(s) independently can be administered in any suitable mode, including without limitation orally, topically (e.g., dermally/epicutaneously, transdermally, mucosally, transmucosally, intranasally [e.g., by nasal spray or drop], opthalmically [e.g., by eye drop], pulmonarily [e.g., by inhalation], bucally, sublingually, rectally and vaginally), by injection or infusion (e.g., parenterally, including intramuscularly, subcutaneously, intradermally, intravenously/intravascularly, and intrathecally), and by implantation (e.g., subcutaneously and intramuscularly). In some embodiments,

an antipruritic agent is administered topically (e.g., dermally) if the pruritus is localized, and is administered systemically (e.g., orally or intravenously) if the pruritus is widespread (generalized) or has a systemic cause. In certain embodiments, serlopitant and/or the optional additional antipruritic agent(s) are administered orally. In other embodiments, serlopitant and/or the optional additional antipruritic agent(s) are administered topically (e.g., dermally, mucosally, bucally or sublingually).

[0091] Serlopitant and the optional additional antipruritic agent(s) independently can be administered in any suitable frequency, including without limitation daily (one, two, three or more times per day), every two days, twice weekly, thrice weekly, weekly, every two weeks, every three weeks, monthly, every two months and every three months. The dosing frequency can depend on, e.g., the mode of administration chosen. For example, a dermal formulation of serlopitant, and/or that of the optional additional antipruritic agent(s), can be applied to the skin of a subject two, three or four times a day. In some embodiments, serlopitant is administered under a chronic dosing regimen. In certain embodiments, serlopitant is administered over a period of at least 2 weeks, 3 weeks, 1 month, 1.5 months, 2 months, 3 months, 4 months, 5 months, 6 months or longer.

[0092] Examples of topical dosage forms include without limitation creams, ointments, gels, liniments, lotions, suppositories (e.g., rectal and vaginal suppositories), buccal and sublingual tablets and pills, sprays (e.g., dermal and nasal sprays), and drops (e.g., eye, nose and ear drops). Non-limiting examples of oral dosage forms include solid dosage forms (e.g., cachets, capsules and tablets) and liquid dosage forms (e.g., solutions or suspensions in an aqueous liquid and/or a non-aqueous liquid, and oil-in-water liquid emulsions or water-in-oil liquid emulsions). In a non-limiting example of a formulation for injection, the formulation is in the form of a solution and comprises an antipruritic agent (e.g., a local anesthetic), a vehicle (e.g., a water-based vehicle or sterile water), a buffer, a reducing agent/antioxidant (e.g., sodium metabisulfite if epinephrine is used as a vasoconstrictor) and a preservative (e.g., methylparaben), and optionally a vasoconstrictor (e.g., epinephrine) to increase the duration of the pharmacological effect of the antipruritic agent by constricting the blood vessels, thereby concentrating the antipruritic agent for an extended duration and increasing the maximum dose of the antipruritic agent.

[0093] Table 4 provides non-limiting examples of combination therapies employing serlopitant and one or more additional antipruritic agents for the treatment of pruritus associated with various conditions. Table 4 may also show other therapeutic agents used to treat the underlying causes of the conditions.

Table 4

Agents in Addition to Serlopitant	Conditions
Corticosteroid	Skin inflammation, chapped skin, atopic dermatitis, contact dermatitis, eczema, seborrheic dermatitis, erythroderma, lichen planus, lichen simplex chronicus, lichen sclerosis, lupus erythematosus, psoriasis, rashes, scabies and burns (e.g., sunburn)
Antihistamine (e.g., doxepin for topical use, and sedating diphenhydramine or non-sedating cetirizine for oral use)	Urticaria, allergy-based pruritus, localized pruritus (e.g., insect bites and stings) and generalized pruritus (e.g., chickenpox)
Local anesthetic + optional counterirritant/ cooling agent	Localized pruritus (e.g., insect bites and stings), and mild to moderate pruritus
Counterirritant (e.g., capsaicin)	Chronic localized pruritus (e.g., notalgia paresthetica and prurigo nodularis)
Moisturizer &/or calamine	Allergic rashes (e.g., poison ivy/oak and urticaria), burns (e.g., sunburn), and insect bites and stings
Moisturizer + optional counterirritant/cooling agent	Atopic dermatitis, contact dermatitis, eczema, seborrheic dermatitis, ichthyosis, psoriasis and xerosis
Immunomodulator (e.g., tacrolimus) + optional corticosteroid	Atopic dermatitis
JAK inhibitor (e.g., tofacitinib) or PDE inhibitor (e.g., apremilast) or vitamin D (e.g., calcipotriol)	Psoriasis
TrkA inhibitor (e.g., CT327)	Atopic dermatitis, psoriasis and cutaneous T-cell lymphoma
JAK inhibitor (e.g., ruxolitinib)	Anemia, peripheral neuropathy and polycythemia vera
Aspirin (topical)	Lichen simplex chronicus
Tricyclic antidepressant (e.g., doxepin)	Chronic severe pruritus
Opioid receptor antagonist (e.g., naloxone)	Intractable pruritus of renal and cholestatic diseases
1) Ultraviolet B phototherapy + erythropoietin; or 2) Cholestyramine + opioid receptor antagonist (e.g., naltrexone) + activated charcoal; or 3) Thalidomide	Chronic renal disease
1) Ion-exchange resin (e.g., cholestyramine) + opioid receptor antagonist (e.g., naloxone); or 2) SSRI, S-adenosyl methionine, rifampicin &/or ursodeoxycholic acid; or	Cholestasis

3) Cholestyramine + opioid receptor antagonist (e.g., nalmefene) + serotonin antagonist (e.g., ondansetron) + ursodeoxycholic acid + rifampicin + optional bright-light therapy; or 4) Ultraviolet B + cannabinoid (e.g., dronabinol)	
1) Counterirritant (e.g., capsaicin) + ultraviolet B phototherapy + optional activated charcoal + optional low pH moisturizer; or 2) Kappa opioid receptor agonist (e.g., nalfurafine) + optional ultraviolet B	Uremia (uremic pruritus)
Ultraviolet B phototherapy	Aquagenic dermatitis, atopic dermatitis, HIV/AIDS and prurigo nodularis
Ultraviolet A phototherapy + psoralen	Eczema, psoriasis, vitiligo and cutaneous T-cell lymphoma
1) Ultraviolet A phototherapy + psoralen; or 2) SSRI (e.g., paroxetine), aspirin &/or interferon alpha	Polycythemia vera
Serotonin receptor antagonist (e.g., ondansetron) (concurrent with opioid) + opioid receptor antagonist (e.g., nalbuphine) (concurrent with opioid)	Spinal opioid-induced pruritus
Antipsychotic (e.g., pimozide) + SSRI (e.g., fluvoxamine)	Pruritic psychiatric disorders (e.g., neurotic excoriation)

Use of Serlopitant as a Sleep Aid

[0094] The invention also encompasses the use of serlopitant as a sleep aid. Accordingly, the invention provides a method of aiding sleep, comprising administering to a subject suffering from a sleep problem or disorder an effective amount of serlopitant or a pharmaceutically acceptable salt, solvate or polymorph thereof. An additional sleep-aiding agent optionally can also be administered to the subject.

[0095] Serlopitant can aid sleep in subjects who suffer from a sleep disorder or a sleep problem in general. As a sleep aid, serlopitant may have a sedative effect (reducing irritability, anxiety or excitement) and/or a hypnotic effect (inducing, sustaining and/or lengthening sleep).

[0096] Examples of sleep disorders that serlopitant can potentially alleviate include without limitation insomnia (including primary and secondary insomnia, and transient, acute and chronic insomnia); sleeping sickness (African trypanosomiasis); circadian rhythm sleep disorders (e.g., advanced sleep phase disorder [ASPD], delayed sleep phase disorder [DSPD], irregular sleep wake rhythm, non-24 hour sleep-wake disorder, jet lag and shift work sleep disorder [SWSD]); parasomnias (e.g., bruxism,

rapid eye movement sleep behavior disorder [RBD], periodic limb movement disorder [PLMD or nocturnal myoclonus], restless legs syndrome [RLS], sleep paralysis, exploding head syndrome, sleep terror [night terror or *Pavor nocturnus*], nocturia, nocturnal eating syndrome, sleep talking [somniloquy], sleepwalking [somnambulism] and somniphobia); and breathing-related sleep disorders (e.g., sleep apnea [including central, obstructive and mixed sleep apnea], hypopnea syndrome, sleep-related hypoventilation, snoring and upper airway resistance syndrome).

[0097] For use as a sleep aid, serlopitant is administered when the subject desires to sleep (e.g., at night or around bedtime). An effective amount of serlopitant is administered to aid sleep. The effective amount may depend on various factors, including the mode of administration; the age, body weight, general health, sex and diet of the subject; the severity of the sleep problem; and the response of the subject to the treatment. In certain embodiments, the dose of serlopitant as a sleep aid is about 0.1-500 mg, or about 0.25-400 mg, or about 0.5-300 mg, or about 1-200 mg, or about 2.5-100 mg, or about 5-50 mg, or as deemed appropriate by the treating physician. A single dose or multiple doses of serlopitant can be administered to aid sleep. In further embodiments, the dosage of serlopitant to aid sleep is about 0.01- 10 mg/kg, 0.025- 7.5 mg/kg, 0.05-5 mg/kg, 0.075-2.5 mg/kg or 0.1-1 mg/kg body weight, or as deemed appropriate by the treating physician.

[0098] Serlopitant can be administered via any suitable route. Potential routes of administration of serlopitant include without limitation oral, parenteral (including intramuscular, subcutaneous, intradermal, intravenous, intraarterial, intramedullary and intrathecal), intraperitoneal, and topical (including dermal/epicutaneous, transdermal, mucosal, transmucosal, intranasal [e.g., by nasal spray or drop], intraocular [e.g., by eye drop], pulmonary [e.g., by inhalation], buccal, sublingual, rectal and vaginal). In certain embodiments, serlopitant is administered orally.

[0099] In other embodiments, serlopitant is administered topically via a buccal or sublingual tablet or pill. The buccal or sublingual tablet or pill can be designed to provide faster release of serlopitant for more rapid uptake of it into systemic circulation. In addition to a therapeutically effective amount of serlopitant, the buccal or sublingual tablet or pill can contain suitable excipients, including without limitation any combination of fillers and diluents (e.g., mannitol and sorbitol), binding agents (e.g., sodium carbonate), wetting agents (e.g., sodium carbonate), disintegrants (e.g., crospovidone and croscarmellose sodium), lubricants (e.g., silicon dioxide [including colloidal silicon dioxide] and sodium stearyl fumarate), stabilizers (e.g., sodium bicarbonate), flavoring agents (e.g., spearmint flavor), sweetening agents (e.g., sucralose), and coloring agents (e.g., yellow iron oxide). A non-limiting example of a patient population that can benefit from a buccal or sublingual tablet or pill of a sleep aid is patients who wake up prematurely and have difficulty falling asleep again.

[00100] In some embodiments, an (one or more) additional sleep-aiding agent is administered in combination with serlopitant to aid sleep. The additional sleep-aiding agent can be administered concurrently with or sequentially to (before or after) administration of serlopitant. If administered concurrently with serlopitant, the additional sleep-aiding agent can be contained in the same composition as serlopitant or in separate compositions. Use of serlopitant may reduce the dosage of and/or the length of treatment with the additional sleep-aiding agent which would otherwise be required and thereby minimize or avoid any adverse effects (e.g., dependence or addiction) of the additional sleep-aiding agent.

[00101] The additional sleep-aiding agent can be selected for its soporific property or for its ability to treat the sleep disorder or the underlying cause of the sleep disorder (e.g., stress, anxiety, depression or a neurological condition). In some embodiments, the additional sleep-aiding agent is selected from the group consisting of hypnotics, sedatives, anxiolytics, antipsychotics and antidepressants. A particular sleep-aiding agent can have pharmacological effects that fall in multiple categories (e.g., benzodiazepines can have a sedative or anxiolytic effect at a lower dose and a hypnotic effect at a higher dose). In further embodiments, the additional sleep-aiding agent is selected from the group consisting of:

antidepressants, including tricyclic antidepressants (e.g., amitriptyline, amitriptylinoxide, amoxapine, clomipramine, desipramine, dosulepin [dothiepin], doxepin, imipramine, lofepramine, melitracen, nortriptyline, protriptyline and trimipramine), tetracyclic antidepressants (e.g., amoxapine, maprotiline, mazindol, mianserin, mirtazapine and setiptiline), selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), serotonin antagonist and reuptake inhibitors (SARIs, e.g., etoperidone, lorpiprazole, lubazodone, mepiprazole, nefazodone and trazodone), serotonin-norepinephrine reuptake inhibitors (SNRIs, e.g., bicifadine, duloxetine, milnacipran, levomilnacipran, sibutramine, venlafaxine, desvenlafaxine and SEP-227162), and monoamine oxidase (MAO) inhibitors (including selective MAO-A inhibitors, such as *moclobemide, pirlindole [pirazidol] and toloxatone [humoryl]*), and analogs and derivatives thereof;

antipsychotics, including first-generation (or typical) antipsychotics (including phenothiazines [e.g., chlorpromazine, fluphenazine, levomepromazine, perazine, pericyazine, perphenazine, pipotiazine, prochlorperazine, promazine, promethazine, thioproperazine, thioridazine and trifluoperazine] and thioxanthenes [e.g., clopenthixol, zuclopenthixol, flupentixol and thiotixene]) and second-generation (or atypical) antipsychotics (e.g., amisulpride, aripiprazole, asenapine, clozapine, iloperidone, loxapine, amoxapine, lurasidone, olanzapine, quetiapine, norquetiapine, risperidone, paliperidone, sertindole, trimipramine, ziprasidone and zotepine), and analogs and derivatives thereof;

antihistamines that inhibit action at the histamine H_1 receptor, including first-generation antihistamines such as alimemazine (trimeprazine), antazoline, azatadine, bromazine, carbinoxamine, chlorpromazine, clemastine, clocinizine, cyclizine, chlorcyclizine, cyproheptadine, dimenhydrinate, dimetindene, diphenhydramine, bromodiphenhydramine, chlorodiphenhydramine, doxylamine, hydroxyzine, meclizine, mepyramine [pyrilamine], methdilazine, oxatomide, phenindamine, pheniramine, brompheniramine, chlorpheniramine, fluorpheniramine, orphenadrine, phenyltoloxamine, promethazine, tripelennamine and triprolidine, and analogs and derivatives thereof;

benzodiazepines that enhance the effect of gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor by positive allosteric modulation of the receptor, such as adinazolam, alprazolam, chlordiazepoxide, climazolam, clonazepam, clorazepate, diazepam, estazolam, etizolam (a benzodiazepine analog), flunitrazepam, flurazepam, halazepam, loprazolam, lorazepam, lormetazepam, midazolam, nimetazepam, nitrazepam, oxazepam, prazepam, quazepam, temazepam and triazolam, and analogs and derivatives thereof;

non-benzodiazepines (also called Z-drugs) that are positive allosteric modulators of the $GABA_A$ receptor, such as beta-carbolines (e.g., abecarnil, gedocarnil and ZK-93423), cyclopyrrolones (e.g., pagoclone, pazinaclone, suproclone, suriclone, zopiclone and eszopiclone,), imidazopyridines (e.g., alpidem, necopidem, saripidem and zolpidem), pyrazolopyrimidines (e.g., divaplon, fasiplon, indiplon, lorediplon, ocinaplon, panadiplon, taniplon and zaleplon), and triazolopyridazines (e.g., CL-218,872), and analogs and derivatives thereof;

barbiturates that are positive allosteric modulators of the $GABA_A$ receptor, such as allobarbital, amobarbital, aprobarbital, alphenal, barbital, brallobarbital, butabarbital, mephobarbital, pentobarbital, phenobarbital, secobarbital and sodium thiopental, and analogs and derivatives thereof;

GABA analogs, such as gabapentin and pregabalin, and analogs and derivatives thereof;

melatonin receptor (e.g., MT_1 and/or MT_2) agonists, such as melatonin, agomelatine, LY-156,735, piromelatine, ramelteon and tasimelteon, and analogs and derivatives thereof;

orexin receptor (e.g., OX_1 and/or OX_2) antagonists, such as almorexant, suvorexant, SB-334,867, SB-408,124, SB-649,868, TCS-OX2-29, and N-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-N-pyridin-3-ylmethyl-acetamide (EMPA), and analogs and derivatives thereof;

4-quinazolinones, such as afloqualone, cloroqualone, diproqualone, etaqualone, mebroqualone, mecloqualone, methaqualone, methylmethaqualone and nitromethaqualone, and analogs and derivatives thereof;

opioids (e.g., for pain-associated sleep disorders), such as buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, methadone, morphine, ethylmorphine, oxycodone,

oxymorphone, pethidine, propoxyphene, dextropropoxyphene, thebaine and tramadol, and analogs and derivatives thereof;

herbs, such as *Cannabis* (including cannabinoids such as cannabidiol [CBD] and tetrahydrocannabinol [THC]), *Duboisia hopwoodii* (pituri), *Humulus lupulus* (hops), *Hypericum perforatum* (St. John's wort), *Lactuca virosa* (opium lettuce), *Lavandula* (lavender), *Matricaria chamomilla* (chamomile), *Nepeta cataria* (catnip), *Passiflora* (passion flowers) (e.g., *P. incarnata*), *Piper methysticum* (kava), *Prostanthera striatiflora* (striped mintbush), *Sceletium tortuosum* (kanna), *Scutellaria* (skullcaps) (e.g., *S. canescens*, *S. cordifolia*, *S. galericulata* and *S. lateriflora*), *Valeriana officinalis* (valerian), and *Withania somnifera* (ashwagandha); and

other kinds of substances, such as S-adenosyl-L-homocysteine, L-tryptophan, L-arginine-L-aspartate, delta sleep-inducing peptide (DSIP), chloral hydrate, ethanol, 2-methyl-2-butanol, gamma-hydroxybutyric acid (GHB), glutethimide, medetomidine, dexmedetomidine, menthyl isovalerate (validol), S32212, α_2 adrenergic agonists (e.g., clonidine), and carbonic anhydrase inhibitors (e.g., acetazolamide and topiramate), and analogs and derivatives thereof.

[00102] The additional sleep-aiding agent can also be selected for its ability to treat a condition that contributes to sleep difficulty (e.g., abnormal bodily movement or behavior). For example, an anticonvulsant can be used in combination with serlopitant to treat a parasomnia, such as restless legs syndrome, periodic limb movement disorder or nocturnal eating syndrome. Examples of anticonvulsants include without limitation carbamazepine, gabapentin, pregabalin, valproic acid and salts thereof (e.g., sodium valproate), and analogs and derivatives thereof.

[00103] The additional sleep-aiding agent can be administered via any suitable mode. In certain embodiments, the additional sleep-aiding agent is administered orally, bucally or sublingually.

Therapeutic Administration and Doses

[00104] The terms "administration of" or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment in a form that can be introduced into that individuals body in a therapeutically useful form and therapeutically effective amount, including, but not limited to, oral dosage forms, such as tablets, capsules, syrups, suspensions, and the like.

[00105] The terms "treat", "treating" and "treatment" of chronic pruritus all refer to reducing the frequency of symptoms of acute or chronic pruritus (including eliminating them entirely), avoiding the occurrence of acute or chronic pruritus and/or reducing the severity of symptoms of acute or chronic pruritus.

[00106] The term "therapeutically effective amount" refers to a sufficient quantity of the compounds of the present invention, in a suitable composition, and in a suitable dosage form to treat the noted disease conditions. The "therapeutically effective amount" will vary depending on the compound, the severity of the condition causing the pruritus, and the age, weight, *etc.*, of the patient to be treated.

[00107] The term "loading dose" refers to the amount of the compounds or compositions of the present invention that is often larger than subsequent doses, administered for the purpose of establishing a therapeutic level of the drug. More generally, a loading dose is the amount of Compound I, or a pharmaceutically acceptable salt, solvate or polymorph thereof, administered to a patient with pruritus given sometime after presentation but before initiation of one or more maintenance doses. Alternatively, a loading dose refers to one or a series of doses that may be given at the onset of therapy to achieve a target concentration of an active ingredient quickly.

[00108] The present methods for treatment of pruritus require administration of serlopitant, or a pharmaceutical composition containing serlopitant, to a patient in need of such treatment. The compound and/or pharmaceutical compositions are preferably administered orally. Various delivery systems are known, (*e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*) can be used to administer a serlopitant compound and/or composition. The compound and/or pharmaceutical compositions may be delivered via sustained release dosage forms.

[00109] The amount of serlopitant, a pharmaceutically acceptable salt, solvate or polymorph thereof, that will be effective in the treatment pruritus in a patient will depend on the specific nature of the condition, and can be determined by standard clinical techniques known in the art. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The specific dose level for any particular individual will depend upon a variety of factors including the activity of the composition, the age, body weight, general physical and mental health, genetic factors, environmental influences, sex, diet, time of administration, route of administration, rate of excretion, and the severity of the pruritus being treated.

[00110] Preferably, the dosage forms are adapted to be administered to a patient three, two or one time a day. More preferably, a therapeutically effective amount is taken once per day. Alternatively, a dose may be taken every other day, every third day, every fourth day or once a week. In some embodiments, serlopitant is administered under a chronic dosing regimen. In certain embodiments, a therapeutically effective amount of serlopitant is administered over a period of at least 2 weeks, 3 weeks, 1 month, 1.5 months, 2 months, 3 months, 4 months, 5 months, 6 months or longer.

[00111] Doses may be taken at any time convenient to the patient. However, to minimize side effects such as dizziness or drowsiness, a daily dose may be taken at bedtime. NK-1 receptor antagonists have been shown to cause drowsiness in human clinical trials for uses other than treating pruritus. For example, Ratti *et al.* reported as much as a doubling in the incidence of somnolence vs. placebo in patients treated with casopitant for major depressive disorder (*J. Clin. Psychopharmacol.*, 2011, **31**:727-733). Somnolence was also seen in a similar clinical trial testing NK-1 receptor antagonist L-759274 as an anti-depressant (M. S. Kramer *et al., Neuropsychopharm.*, 2004, **29**:385-392). Thus, in one embodiment of the present invention, serlopitant is administered before the patient goes to bed.

[00112] Dosing may be provided alone or in combination with other drugs and may continue as long as required for effective treatment pruritus. For example, the compounds of the present invention may be administered in combination with another substance that has a complimentary effect to the tachykinin and substance P inhibitory effect of the present invention. Appropriate compounds include other NK-1 receptor antagonists such as, but not limited to, casopitant (GW679769), L-759274, L-733060, CP122,721, BIIF 1149CL, DNK333, M516102, ezlopitant, rolapitant, orvepitant, LY-686017, lanepitant (LY-303870), maropitant, vestipitant, vofopitant, aprepitant, fosaprepitant, AV-818, and TA-5538.

[00113] Dosage ranges of compounds of the present invention for oral administration may be stated in terms of amount of drug administered per time period. A certain amount of active ingredient may be given one or more times a day as appropriate according to the factors described above. For example, doses may be taken once a day, twice a day, three times a day, four times a day, or more. Suitable dosages range from about 0.1 mg to about 30 mg, and preferably, from about 1 mg to about 7.5 mg. Suitable dosages are typically 0.10 mg, 0.15 mg, 0.20 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 100 mg or 200 mg one or more times a day. Preferably, a dose of 0.25 mg, 1 mg or 5 mg is administered once a day.

[00114] Alternatively, suitable dosage ranges of compounds of the present invention for oral administration are generally about 0.001 mg to about 500 mg of drug per kilogram body weight, preferably from about 0.1 mg to about 200 mg of drug per kilogram body weight, and more preferably about 1 to about 100 mg/kg-body wt. per day. Dosage ranges may be readily determined by methods known to the skilled artisan. The amount of active ingredient that may be, for instance, combined with carrier materials to produce a single dosage form will vary depending upon the patient treated and the particular mode of administration. Dosage unit forms will generally contain between about 0.25 mg to about 500 mg of active ingredient.

[00115] In cases in which longer-term persistence of active drug is desirable, for example but not limited to, in the treatment of chronic pruritus, a dosing schedule is used where a loading dose is administered, followed by either (i) a second loading dose, or doses, and a maintenance dose (or doses), or (ii) a maintenance dose or doses, without a second loading dose, as determined to be appropriate by one skilled in the art. The schedule for administration of the loading and maintenance doses may be determined based upon the individual requirements of a particular patient. In one embodiment of the present invention, one loading dose is administered, followed by administration of a therapeutically effective maintenance dose after an appropriate interval, such as after one day. In another embodiment, a loading dose is administered on day 1, a second loading dose on day 2, and the maintenance dose is administered on day 3 and thereafter for the duration of therapy. The loading dose may be five, four, three or two times the maintenance dose. Preferably, the loading dose is three times the maintenance dose. The active drug can be administered via any suitable mode (e.g., orally).

Determination of Therapeutic Effectiveness

[00116] The effectiveness of compositions of the present invention can be tested in experimental animal models of pruritus known to those skilled in the art. For example, various mouse models have been utilized to evaluate treatments for itching. Tsukumo *et al.* describe a model in which 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (oxazolone) induces chronic dermatitis with an associated itch response in BALB/c mice that can be used to determine whether an anti-pruritic treatment is effective (*J. Pharmacol. Sci.*, 2010, **113**:255-262). Costa *et al.* report a similar model in which *Phoneutria nigriventer* spider venom is used as the itch inducer (*Vascul. Pharmacol.*, 2006, **45**(4):209-14). Analogously, Ohmura *et al.* use picrylchloride in NC/Nga mice to stimulate scratching behavior (*Eur. J. Pharmacol.*, 2004; **491**:191–194). Essentially, itching is induced in the subject animal with an irritating agent, the test compound or a placebo is administered, and the animal observed under controlled conditions. Scratching behavior is quantified and analyzed using standard statistical techniques. A test compound is considered effective if either continuous or severe scratching is suppressed.

[00117] The efficacy of the methods and compositions of the present invention in the treatment of acute and chronic pruritus can also optionally be evaluated in human clinical trials conducted under appropriate standards and ethical guidelines as set forth by the U.S. Food and Drug Administration (FDA). After the general safety of a drug is determined in Phase I clinical trials conducted in healthy volunteers, Phase II trials assessing the safety and efficacy of the drug in patients with the condition being treated are conducted. Typically, such trials are double-blinded and placebo-controlled, and may

be dose-ranging. Phase III studies gather more information about safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs.

[00118] Because amelioration of pruritus is subject to a patient's own perceptions, it can be difficult to evaluate with typical clinical endpoints. However, two standardized assessment tools have been created and may be used in clinical trials demonstrating the utility of the present invention. The Visual Analog Scale (VAS) is the most commonly used tool to evaluate the intensity of pruritus (N. Q. Phan *et al., Acta Derm. Venereol.*, 2012; **92**:502-507). The VAS is a graphic tool with a 100-mm horizontal line with the left end labeled "no symptom" and the right end labeled "worst imaginable symptom". The patient is asked to draw a vertical line to indicate the horizontal scale at a point that corresponded to the intensity of the symptom. The length from the left end to the vertical mark made by the patient is measured in millimeters. Separation in one-hundredths is regarded as sufficiently sensitive (R. C. Aitken, *Proc. R. Soc. Med.*, 1969, **62**:989–993). The results may be analyzed using standard statistical techniques known to those skilled in the art.

[00119] In addition to the VAS, the Dermatology Life Quality Index (DLQI) may be used to evaluate the efficacy of a chronic pruritus treatment. The DLQI, a self-administered general dermatology quality of life questionnaire, was originally developed and published in a dermatology clinic at University Hospital of Wales (A. Y. Finlay and G. K. Khan, *Clin. Exper. Derm.*, 1994,**19**:210-216). Independent studies have verified that the DLQI is an easy and efficient method for assessing quality of life in dermatology patients (H. B. Hahn *et al., J. Am. Acad. Dermatol.*, 2001, **45**(1):44-8). A current version of the simple, ten-question validated questionnaire, with instructions for use and scoring is available from the School of Medicine, Cardiff University, Wales, UK (world wide web URL dermatology.org.uk/quality/).

[00120] The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

[00121] All of the inactive pharmaceutical ingredients in the examples below comply with United States Pharmacopeia and The National Formulary requirements and are tested and released according to the monograph for each ingredient specified in the USP/NF compendium.

Example 1. Preparation of Serlopitant Tablets

[00122] Serlopitant, 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-4-(4-fluorophenyl)-1,3,3a,4,5,6,7,7a-octahydroisoindol-2-yl]cyclopent-2-en-1-one, Compound 1, may be formulated as a tablet for oral use. Table 1 shows the qualitative/quantitative composition of exemplary

dosages. Minor variations in the excipient quantities (+/-10 %) may occur during the drug development process.

Table 1

Components	Function	% of composition
Compound 1	Active agent	1-6 %
Microcrystalline cellulose	Diluent	50-60%
Mannitol	Diluent	20-30%
Croscarmellose Sodium	Disintegrant	1-3%
Colloidal silica	Disintegrant	0.25-0.5%
Sodium Lauryl Sulfate	Surfactant	5-6%
Magnesium Stearate	Lubricant	0.25-2%
Total Tablet Composition		100%

[00123] Tablet potencies of 0.25, 1 and 5 mg are prepared as a compressed tablet formulation. The tablet manufacturing process is the same for all proposed potencies. The process consists of the following steps: 1) Compound 1, mannitol and sodium lauryl sulfate are blended; 2) the remaining mannitol is added to the blender and mixed; 3) microcrystalline cellulose, croscarmellose sodium, and colloidal silica are added to the blender containing the mixture above to complete the mixing and the blend is de-agglomerated if necessary; 4) the blend is lubricated with magnesium stearate which has been previously screened, if necessary; 5) the lubricated blend is roller compacted and milled, and then lubricated with magnesium stearate, which has been previously screened, if necessary; and 6) the mixture is then compressed into tablets of the appropriate weight.

Example 2. Preparation of Serlopitant Capsules

[00124] Serlopitant (Compound 1) may also be supplied to the clinic as liquid-filled capsules. Table 2 shows the qualitative/quantitative composition of exemplary dosages. Minor variations in the excipient quantities (+/-10 %) may occur during the drug development process.

Table 2

Components	Function	Unit Strength		
		0.25 mg	1 mg	4 mg
Capsule Fill				
Compound 1	Active agent	0.25 mg	1 mg	4 mg
Mono- & Di-glycerides	Solubilizer	399 mg	398.6 mg	395.6 mg

Butylated Hydroxyanisole	Antioxidant	0.40 mg	0.40 mg	0.40 mg
Capsule Shell				
#0 White Opaque Hard Gelatin Capsule*	Capsule shell	96 mg**	96 mg**	96 mg**
Gelatin***	Banding component	---	---	---
Polysorbate 80***	Banding component	---	---	---

*Capsules are provided by Capsugel (Morristown, NJ) and contain gelatin and titanium dioxide

**Approximate weight of empty capsule shell

***As needed to seal the capsule shells

[00125] The formulation is prepared by dissolving the drug substance in mono- and di-glycerides. Furthermore, 0.1 wt% butylated hydroxyanisole is added as an antioxidant. Initial capsule strengths are dispensed into hard gelatin capsules and sealed by spraying with a 1:1 (wt/wt) water:ethanol solution. Subsequent potencies including 0.25, 1, and 4 mg are dispensed into hard gelatin capsules and sealed with a band of gelatin/polysorbate 80. Corresponding placebo formulations are prepared in a similar manner, but without the addition of the drug substance and the antioxidant.

[00126] The capsule manufacturing process is the same for all potencies. The process consists of the following steps: 1) the mono- and di-glycerides excipient is melted at 40°C, if necessary; 2) the mono- and diglycerides are added to an appropriately sized, jacketed vessel and mixing is initiated; 3) the butylated hydroxyanisole is added to the mono- and di-glycerides and mixed until dissolved (minimum of 10 min); 4) Compound 1 is slowly added to the mixture and mixed until dissolved (visual confirmation); 5) the solution is filled into hard gelatin capsules; 6) the filled capsules are sealed with a mixture of gelatin and polysorbate 80; 7) the sealed capsules are allowed to dry overnight and then the capsules are visually inspected for leaking; 8) the acceptable capsules may be weighed sorted, if necessary; and 9) the finished product is then packaged in appropriate containers.

Example 3. Clinical Study of Serlopitant in Chronic Pruritus

[00127] A well-controlled human clinical trial testing the efficacy of three dosages of serlopitant in the treatment of chronic pruritus is conducted in accordance with the ICH Guidelines for Good Clinical Practices, the U.S. Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA), and any local regulatory requirements. The study is a Phase II randomized, double-blind, parallel group, placebo-controlled, multicenter trial designed to test the efficacy and safety of several doses of serlopitant versus placebo in patients with chronic pruritus. The study patient population

includes adult, males or females, 18 to 72 years of age. The patients must be previously diagnosed with chronic pruritus caused by any etiology, except uremia, hepatic failure, cancer or cancer therapy, with chronic pruritus defined as greater than 6 weeks of itching and a VAS score of greater than 7.

[00128] Patients are randomized to receive either placebo or one of three doses of active agent. Patients take active drug or placebo once daily by mouth for a total of 2 to 8 weeks. The maximum study duration for each subject is approximately 14 weeks and includes a screening period of up to 2 weeks, a treatment period of 2-8 weeks, and a follow-up period of up to 4 weeks. The study parameters are summarized in Table 3.

Table 3

Study Title:	Phase II Study of Serlopitant In Patients with Chronic Pruritus
Development Phase:	Phase II
Study Objectives:	Dose finding, efficacy and safety
Study Design:	Multicenter, double blind, parallel group, dose finding
Sample Size:	80-240 subjects evaluable for analysis
Study Population:	Patients with chronic pruritus (over 6 weeks duration) unresponsive to standard treatment
Investigational Product:	Oral daily tablet
	Dosage and frequency: Day 1: loading dose of 3 times of drug dose (0.25 mg, 1 mg, or 5 mg), followed by Drug A, Drug B, or Drug C Drug A: 0.25 mg serlopitant daily for 2 to 8 weeks Drug B: 1 mg serlopitant daily for 2 to 8 weeks Drug C: 5 mg serlopitant daily for 2 to 8 weeks
Reference Product(s):	None
Control Product(s):	Matching placebo daily for 2 to 8 weeks
Efficacy Evaluation Criteria:	Efficacy is measured daily by patient diary. Patients record pruritus level on a 10 point VAS scale. Clinical response is measured by a change in VAS score between the active agent and the placebo. Secondary endpoints will include measures of the Dermatology Life Quality Index (DLQI),lesion healing, and patient and physician global assessments.
Safety Evaluation Criteria:	All local and systemic adverse events observed by or reported to the investigators are evaluated. The intensity, duration, and causal relationship to the study product are rated for all adverse events.
Statistical Methods:	The primary study endpoint is the difference in VAS score at baseline and on treatment between placebo and active agent.
Study Sites:	Multicenter

[00129] Additional clinical trials according to a similar design may be conducted to test different dosage levels of the active ingredient or to differentiate between optimal doses or dosing schedules. Further, the efficacy of the drug in specific populations, such as the elderly, children, or patients with uremia, hepatic failure, cancer or patients undergoing cancer therapy, may be determined in additional clinical trials conducted in a similar fashion.

Example 4. Topical Formulations Containing Serlopitant

[00130] Table 5 shows various topical formulations containing serlopitant. The formulations contain Vanicream™ Moisturizing Skin Cream ("VM"), Vanicream™ Lite Lotion ("VLL") or Aquaphor® Healing Ointment ("AP", from Eucerin) as the base or carrier. VM and VLL are oil-in-water emulsion and AP has an oil base. A stock solution of free base serlopitant (Compound 1, or "Cpd 1") in ethanol (EtOH) was prepared by dissolving free base serlopitant in ethanol to the maximum extent and then filtering the resulting solution through an Anotop® 25 inorganic filter having a 0.02 micron pore size. Free base serlopitant has a maximum solubility in ethanol of 64.5 mg/g EtOH, or 6.45% w/w. To prepare a topical formulation, the stock solution of serlopitant/ethanol was added to a tared tube containing a particular amount of the base until the resulting mixture weighed 25.0 g. The mixture was mixed vigorously for 2 minutes using a vibration stand and then was rotated slowly for 4 days. For the "C" formulations, ethanol containing no serlopitant was added so that the "B" and "C" formulations would contain the same amount of base and ethanol.

Table 5

Mixture	Lot Size (g)	Base (g)	Cpd 1/EtOH Stock Soln (g)	Blank EtOH (g)	% Cpd 1 (w/w)	% EtOH (w/w)
VM-A	25.0	23.06	1.94	0.0	0.5	7.8
VM-B	25.0	21.12	3.88	0.0	1.0	15.5
VM-C	25.0	21.12	1.94	1.94	0.5	15.5
VLL-A	25.0	23.06	1.94	0.0	0.5	7.8
VLL-B	25.0	21.12	3.88	0.0	1.0	15.5
VLL-C	25.0	21.12	1.94	1.94	0.5	15.5
AP-A	25.0	23.06	1.94	0.0	0.5	7.8
AP-B	25.0	21.12	3.88	0.0	1.0	15.5
AP-C	25.0	21.12	1.94	1.94	0.5	15.5

[00131] AP was determined to be an unsuitable base for an ethanol solution containing serlopitant because of ethanol insolubility in that base. The VM base appeared stable/unchanged under 15x

microscopic magnification after 4 days of mixing with 15.5% ethanol. The VLL base showed some aggregation of lamellar structures under 15x microscopic magnification after 4 days of mixing with 15.5% ethanol, but the overall change to the base appeared minor. The VM and VLL formulations can be tested, e.g., for the skin permeation of serlopitant.

Example 5. *In Vitro* Skin Permeation of Serlopitant in Topical Formulations

[00132] Topical formulations A-D used in the *in vitro* skin permeation studies are shown in Table 6. The bases "VM" and "VLL" of formulations A-D are described in Example 4. Formulations A-D were prepared according to the procedures described in Example 4.

Table 6

Formul'n (Base)	Final Mass (g)	Base (g)	Cpd 1/EtOH Stock Soln (g)	Blank EtOH (g)	% Cpd 1 (w/w)	% EtOH (w/w)
A (VM)	25.28	21.27	0.0	4.01	0.0	15.9
B (VLL)	25.12	21.19	3.93	0.0	1.0	15.6
C (VM)	13.80	11.63	2.17	0.0	1.0	15.7
D (VLL)	25.02	21.15	0.0	3.87	0.0	15.5

[00133] *In vitro* skin permeation of serlopitant in topical formulations A-D was evaluated using a Franz diffusion cell. **FIG. 2** illustrates a Franz diffusion cell. A Franz diffusion cell having a circular permeation area of 4.15 cm^2 and a receptor chamber volume of 19 mL was set up with a thermo-regulated outer water jacket to maintain the temperature at 37 °C. The receptor chamber was filled with 19 mL 1×PBS (pH 7.5) containing 10% ethanol and 1% Tween® 80. Solubility test indicated that serlopitant remained soluble at concentrations of 0.5, 5 and 50 ug/mL in this solution after 1 hour of incubation at 37 °C. The solubility of serlopitant decreased significantly if Tween® 80 was not used and decreased slightly if ethanol was not used.

[00134] Human skin was pretreated to remove all subcutaneous fat and was cleaned with 70% ethanol before use. The skin was visually inspected to ensure that it was free of any surface irregularity or small holes and was equally divided into four pieces. The skin was then mounted onto the receptor chamber with the stratum corneum side facing up. About 100 mg of topical formulation A, B, C or D was applied to the skin (actual weight: A, 103.8 mg; B, 101.3 mg; C, 103.2 mg; and D, 103.8 mg), which was then covered with parafilm to avoid evaporation.

[00135] About 0.5 mL of solution was withdrawn through the sampling port of the Franz diffusion cell at 0.5, 1, 2, 4, 6, 18 and 22 hours. The receptor chamber was replenished with equal volume of fresh

diffusion buffer after each sampling. At the end of the experiment (after 22 hours of incubation), the skin was wiped clean with methanol, and the formulation-treated area was weighed and frozen for cryosectioning.

[00136] All samples were processed by solid-phase extraction (SPE) before LC-MS/MS analysis. Briefly, a Strata-X 33 um Polymeric Reverse-Phase column with 30 mg sorbent mass /1 mL volume (Phenomenex) was conditioned with 1 mL of methanol and equilibrated with 1 mL of water. 300 uL of sample was loaded to the column followed by a wash with 1 mL of 30% methanol. Serlopitant was eluted with 2% formic acid in acetonitrile. The sample then was concentrated by blow drying with nitrogen and re-suspended in 50 uL of 50% methanol. A working standard was first generated by spiking the diffusion buffer with known concentrations of serlopitant, which was then processed using the same SPE method. A sensitivity of 0.1 ng/mL was achieved. Serlopitant concentrations in samples resulting from formulations A-D were determined by comparison to the standard. Serlopitant was not detected in samples resulting from topical formulations A and D, as expected. **FIG. 3** shows the cumulative release of serlopitant from topical formulations B and C into the receptor chamber at 0.5, 1, 2, 4, 6, 18 and 22 hours. After an initial lag, serlopitant was detected by LC-MS/MS in the receptor chamber at 6 hours. FIG. 3 indicates that topical formulation B resulted in greater penetration of serlopitant through the skin than topical formulation C in this *in vitro* study.

[00137] The amount of serlopitant retained in the skin was determined at the end of the experiment. The skin was wiped and washed with methanol. The formulation-treated area was cut into horizontal sections of 25 um using a cryostat. Every 10 sections were pooled, placed in Eppendorf tubes, weighed and digested with twice the volume of 1 mg/mL liberase at 37 °C for 1 hour. Digested skin sections were further homogenized with a probe sonicator. To 25 uL of the skin homogenate were added 25 uL of 50% methanol and 100 uL of acetonitrile/methanol to extract serlopitant. For spiked standards, 25 uL of a solution of serlopitant in 50% methanol (from 5 ng/mL to 5000 ng/mL) was added to 25 uL of blank skin homogenate followed by 100 uL of acetonitrile/methanol. Extracted serlopitant was quantified by LC-MS/MS. **FIG. 4** shows the amount of serlopitant (called "VPD737" in FIG. 4) retained in the skin at the end of the experiment. Each bar represents ug of serlopitant/g of skin in 250 um skin layers. For each of topical formulations B and C, the bars from left to right represent the amount of serlopitant retained in skin layers from the stratum corneum to the dermis.

Example 6. Representative Topical Formulations Containing Serlopitant

[00138] **Table 7** provides non-limiting examples of topical formulations that can be prepared with serlopitant or a salt, solvate or polymorph thereof, and optionally an additional therapeutic agent.

Table 7

Dosage Form	Ingredients in Addition to Serlopitant
cream	sorbitol, cetyl alcohol, isopropyl myristate, glyceryl stearate, PEG-100 stearate, petrolatum, benzyl alcohol, titanium dioxide and water
cream	propylene glycol, cetostearyl alcohol, Cremophor® A6, Cremophor® A25, liquid paraffin, parabens and water
cream	glycerol, sorbitol, isopropyl palmitate, emulsifying wax, benzyl alcohol, a pH adjuster (e.g., NaOH or lactic acid), and water
cream	glycerol, stearic acid, glyceryl monostearate, triethanolamine, parabens and water
cream	propylene glycol, cetostearyl alcohol, mineral oil, white petrolatum, ceteareth-30, chlorocresol, sodium phosphate monobasic, phosphoric acid, water, and optionally NaOH
cream	glycerol, cetostearyl alcohol, mineral oil, petrolatum, ceteth-20, diazolidinyl urea, dichlorobenzyl alcohol, edetic acid (EDTA) or disodium edetate, dibasic sodium phosphate and water
cream	propylene glycol, stearyl alcohol, white petrolatum, polysorbate 60, parabens, and optionally water
cream	propylene glycol, stearyl alcohol, cetyl alcohol, oleyl alcohol, mono-, di- and/or tri-glycerides, sodium cetostearyl sulphate, benzyl alcohol, citric acid, a pH adjuster (e.g., NaOH or lactic acid), and water
cream	hexylene glycol, stearyl alcohol, propylene glycol stearate, white wax, white petrolatum, aluminum starch octenylsuccinate, ceteareth-20, titanium dioxide, phosphoric acid and water
cream	propylene glycol, sorbitol, glyceryl monoisostearate, polyglyceryl-3 oleate, mineral oil, microcrystalline wax, colloidal silicon dioxide, parabens, EDTA or disodium edetate, and water
cream	propylene glycol, stearic acid, isopropyl palmitate, emulsifying wax, beeswax, polysorbate 60, an antioxidant (e.g., propyl gallate), a preservative (e.g., sorbic acid and/or potassium sorbate), a pH adjuster (e.g., NaOH and/or citric acid), and water
cream	cetostearyl alcohol, lanolin alcohols, isopropyl myristate, aluminum stearate, magnesium stearate, mineral oil, white petrolatum, water, and optionally disodium edetate and/or lactic acid
cream	propylene glycol, cetostearyl alcohol, white soft paraffin, liquid paraffin, lanolin, simethicone M30, Tween® 60, parabens and water
cream	cetostearyl alcohol, mineral oil, white petrolatum, ceteth-20, parabens, citric acid, sodium citrate, and water
cream	propylene glycol, cetostearyl alcohol, polyoxyl 20 cetostearyl ether, mineral oil (liquid paraffin), petrolatum (white soft paraffin), chlorocresol, parabens, sodium phosphate monobasic, and water

cream	propylene glycol, cetostearyl alcohol, stearic acid, cetyl palmitate, sorbitan monostearate, mineral oil, polysorbate 60, benzyl alcohol and water
ointment	hexylene glycol, propylene glycol stearate, white wax, white petrolatum, phosphoric acid and water
ointment	propylene glycol, mineral oil, petrolatum, steareth-2, tocopherol, EDTA or disodium edetate, dibasic sodium phosphate and water
ointment	propylene glycol, fatty alcohol citrate, fatty acid pentaerythritol ester, sorbitan sesquioleate, white petrolatum, beeswax, aluminum stearate, butylated hydroxyanisole (BHA), citric acid, and optionally water
ointment	an alcohol (e.g., ethanol and/or propylene glycol), polyethylene or white petrolatum, mineral oil, and optionally water
gel	ethanol, carbomer 934P, triethanolamine and water
gel	glycerol, carbomer 940, poloxamer, dimethicone, disodium lauryl sulfosuccinate, silicon dioxide, a preservative (e.g., benzoyl peroxide and/or methyl paraben), EDTA or disodium edetate, a pH adjuster (e.g., NaOH or lactic acid), and water
gel	glycerol, hydroxy-beta-cyclodextrin, hydroxyethyl cellulose, parabens, EDTA or disodium edetate, and water
gel	propylene glycol, polyacrylic acid, medium-chain triglycerides, lecithin, polysorbate 80, a preservative (e.g., benzoic acid), EDTA or disodium edetate, a pH adjuster (e.g., NaOH or lactic acid), and water
gel	ethanol, isopropyl myristate, carbomer 940, triethanolamine, docusate sodium, EDTA or disodium edetate, and water
gel	propylene glycol, Carbopol® 941, PEG 400, methyl paraben, a pH adjuster (e.g., NaOH or lactic acid), and water
gel	propylene glycol, PEG 400, carbomer 934P, allantoin, methyl paraben, a pH adjuster (e.g., NaOH or lactic acid), and water
gel	an alcohol (e.g., ethanol and/or propylene glycol), carbomer, dioctyl sodium sulfosuccinate, a preservative (e.g., benzoyl peroxide), a pH adjuster (e.g., NaOH or lactic acid), and water
gel	glycerol, propylene glycol, aloe vera gel, diazolidinyl urea, capryl/capramidopropyl betaine, parabens, citric acid, sodium citrate, and water
gel	ethanol, hydroxypropyl cellulose and water
lotion	glycerol, stearyl alcohol, glyceryl stearate, PEG-100 stearate, PEG 400, carbomer 941, cyclomethicone, light mineral oil, steareth-21, benzyl alcohol, sorbic acid or potassium sorbate, a pH adjuster (e.g., NaOH or lactic acid), and water
lotion	isopropanol, propylene glycol, hydroxypropyl cellulose, sodium phosphate monobasic, phosphoric acid and water
lotion	propylene glycol, cetyl alcohol, stearyl alcohol, glyceryl stearate, sorbitan monostearate, light mineral oil, sodium lauryl sulfate, parabens, EDTA or disodium edetate, water, and optionally a pH adjuster (e.g., NaOH or citric acid)

lotion	glycerol, cetostearyl alcohol, isostearyl alcohol, stearic acid, glyceryl stearate, sodium lauroyl sarcosinate, methyl paraben and water
suppo-sitory	an alcohol (e.g., ethanol and/or propylene glycol) and glycerides of saturated fatty acids
suppo-sitory	95% ethanol and Suppocire® AM (glyceride base containing saturated C_8-C_{18} triglyceride fatty acids)
pledget	isopropanol, propylene glycol and water
foam	ethanol, propylene glycol, cetyl alcohol, stearyl alcohol, polysorbate 60, KOH and water, and pressurized with a propane/butane propellant
spray (dermal)	ethanol, undecylenic acid, isopropyl myristate, sodium lauryl sulfate, and water
spray (dermal)	glycerol, lactose, cetostearyl alcohol, mineral oil, ceteth-20 phosphate, dicetyl phosphate, urea, potassium phosphate monobasic, parabens, a pH adjuster (e.g., NaOH or lactic acid), and water
spray (nasal)	microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose, polysorbate 80, disodium edetate, potassium sorbate, a pH adjuster (e.g., HCl), water, and optionally an alcohol (e.g., ethanol)
spray (nasal)	microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose, polysorbate 80, benzalkonium chloride, phenylethyl alcohol, water, and optionally an alcohol (e.g., ethanol)
spray (nasal)	hypromellose, benzalkonium chloride, NaCl, EDTA, citric acid, sodium phosphate dibasic, water, and optionally an alcohol (e.g., ethanol)

[00139] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

[00140] From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

What is claimed is:

1. A method of treating pruritus in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-4-(4-fluorophenyl)-1,3,3a,4,5,6,7,7a-octahydroisoindol-2-yl]cyclopent-2-en-1-one (serlopitant) or a pharmaceutically acceptable salt, solvate or polymorph thereof.

2. The method of claim 1, wherein the therapeutically effective amount comprises a dosage of 0.10 mg, 0.15 mg, 0.20 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg one or more times a day.

3. The method of claim 2, wherein the therapeutically effective amount comprises a dosage of 0.25 mg, 1 mg, or 5 mg once a day.

4. The method of claim 1, wherein the therapeutically effective amount comprises a dosage of from about 0.1 mg to about 30 mg or from about 1 mg to about 7.5 mg.

5. The method of claim 1, wherein the therapeutically effective amount is administered orally in the form of a tablet.

6. The method of claim 1, wherein the therapeutically effective amount is administered once a day at bedtime.

7. The method of claim 1, wherein the therapeutically effective amount is administered once a day, once every other day, once every third day, once every fourth day, or once a week.

8. A method of treating pruritus, said method comprising administering 3-[(3a*R*,4*R*,5*S*,7a*S*)-5-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-4-(4-fluorophenyl)-1,3,3a,4,5,6,7,7a-octahydroisoindol-2-yl]cyclopent-2-en-1-one (serlopitant) or a pharmaceutically acceptable salt, solvate or polymorph thereof to a patient in need of such treatment according to a schedule, said schedule comprising:

a) first administering a least one loading dose; and

b) second administering at least one therapeutically effective maintenance dose.

9. The method according to claim 8, wherein the loading dose is five times, four times, three times, or two times the maintenance dose.

10. The method according to claim 9, wherein the loading dose is three times the maintenance dose.

11. The method according to claim 8, wherein the loading dose is administered on day 1 and the maintenance dose is administered on day 2 and thereafter.

12. The method according to claim 8, wherein the loading dose and the maintenance dose are administered at bedtime.

13. The method according to claim 8, further comprising administering a second loading dose prior to administering the maintenance dose.

14. The method according to claim 13, wherein the loading dose is three times the maintenance dose and the second loading dose is two times the maintenance dose.

15. The method of claim 8, wherein the therapeutically effective maintenance dose is 0.10 mg, 0.15 mg, 0.20 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg administered one or more times a day.

16. The method of claim 15, wherein the therapeutically effective maintenance dose comprises a dosage of 0.25 mg, 1 mg, or 5 mg administered once a day.

17. The method of claim 8, wherein the therapeutically effective maintenance dose comprises a dosage from about 0.1 mg to about 30 mg or from about 1 mg to about 7.5 mg.

18. The method of claim 8, wherein the therapeutically effective maintenance dose is administered once a day, once every other day, once every third day, once every fourth day, or once a week.

19. The method of claim 8, wherein serlopitant is administered orally.

20. The method of claim 1 or 8, wherein a therapeutically effective amount, or a therapeutically effective maintenance dose, of serlopitant is administered over a period of at least two weeks.

21. The method of claim 1 or 8, wherein the pruritus is associated with prurigo, a genetic disease or a liver disease.

22. The method of claim 21, wherein the prurigo is prurigo nodularis, the genetic disease is epidermolysis bullosa, and the liver disease is liver failure.

23. The method of claim 1 or 8, wherein serlopitant is administered topically.

24. The method of claim 23, wherein serlopitant is administered dermally or transdermally.

25. The method of claim 1 or 8, further comprising administering one or more additional antipruritic agents.

26. The method of claim 25, wherein the one or more additional antipruritic agents are selected from the group consisting of antihistamines, corticosteroids, immunomodulators, immunosuppressants, antidepressants and anticonvulsants.

27. The method of claim 26, wherein:

the antihistamines are non-sedating second-generation and third-generation antihistamines, such as acrivastine, astemizole, azelastine, bepotastine, bilastine, cetirizine, levocetirizine, ebastine, fexofenadine, ketotifen, levocabastine, loratadine, desloratadine, mizolastine, olopatadine, quifenadine, rupatadine and terfenadine;

the corticosteroids are corticosteroids having moderate or medium potency, such as amcinonide 0.1% (e.g., cream), betamethasone dipropionate 0.05% (e.g., Diprosone® cream/ointment), betamethasone valerate 0.1% (e.g., cream/ointment), clobetasone butyrate 0.05% (e.g., Eumovate® cream), desonide 0.05% (e.g., Tridesilon® cream/ointment and DesOwen® cream/ointment), fluocinolone acetonide 0.01-0.2% (e.g., Synalar® cream/ointment and Synemol® cream), flurandrenolide 0.05% (e.g., Cordran® tape), fluticasone propionate 0.005% (e.g., Cutivate® ointment), fluticasone propionate 0.05% (e.g., Cutivate® cream), halometasone 0.05% (e.g., cream), hydrocortisone butyrate 0.1% (e.g., Locoid® cream/ointment), hydrocortisone valerate 0.2% (e.g., Westcort® cream/ointment), mometasone furoate 0.1% (e.g., Elocon® cream/ointment), triamcinolone acetonide 0.025-0.5% (e.g., Aristocort® cream/ointment, Kenacomb® cream/ointment, Kenalog® cream and Viaderm® KC cream/ointment), and triamcinolone diacetate 0.5% (e.g., cream/ointment);

the immunomodulators and immunosuppressants are selected from antimetabolites (e.g., methotrexate) and calcineurin inhibitors (e.g., cyclosporin, pimecrolimus and tacrolimus);

the antidepressants are serotonin-norepinephrine reuptake inhibitors, such as bicifadine, duloxetine, milnacipran, levomilnacipran, sibutramine, venlafaxine and desvenlafaxine; and

the anticonvulsants are selected from carbamazepine, gabapentin, pregabalin, and valproic acid and salts thereof (e.g., sodium valproate).

28. The method of any one of claims 25 to 27, wherein the one or more additional antipruritic agents are administered topically.

29. The method of claim 28, wherein the one or more additional antipruritic agents are administered dermally or transdermally.

30. A method of aiding sleep, comprising administering to a subject suffering from a sleep problem or disorder an effective amount of serlopitant or a pharmaceutically acceptable salt, solvate or polymorph thereof, and optionally an additional sleep-aiding agent.

31. The method of claim 30, wherein serlopitant and the optional additional sleep-aiding agent are administered orally, bucally or sublingually.

FIG. 1

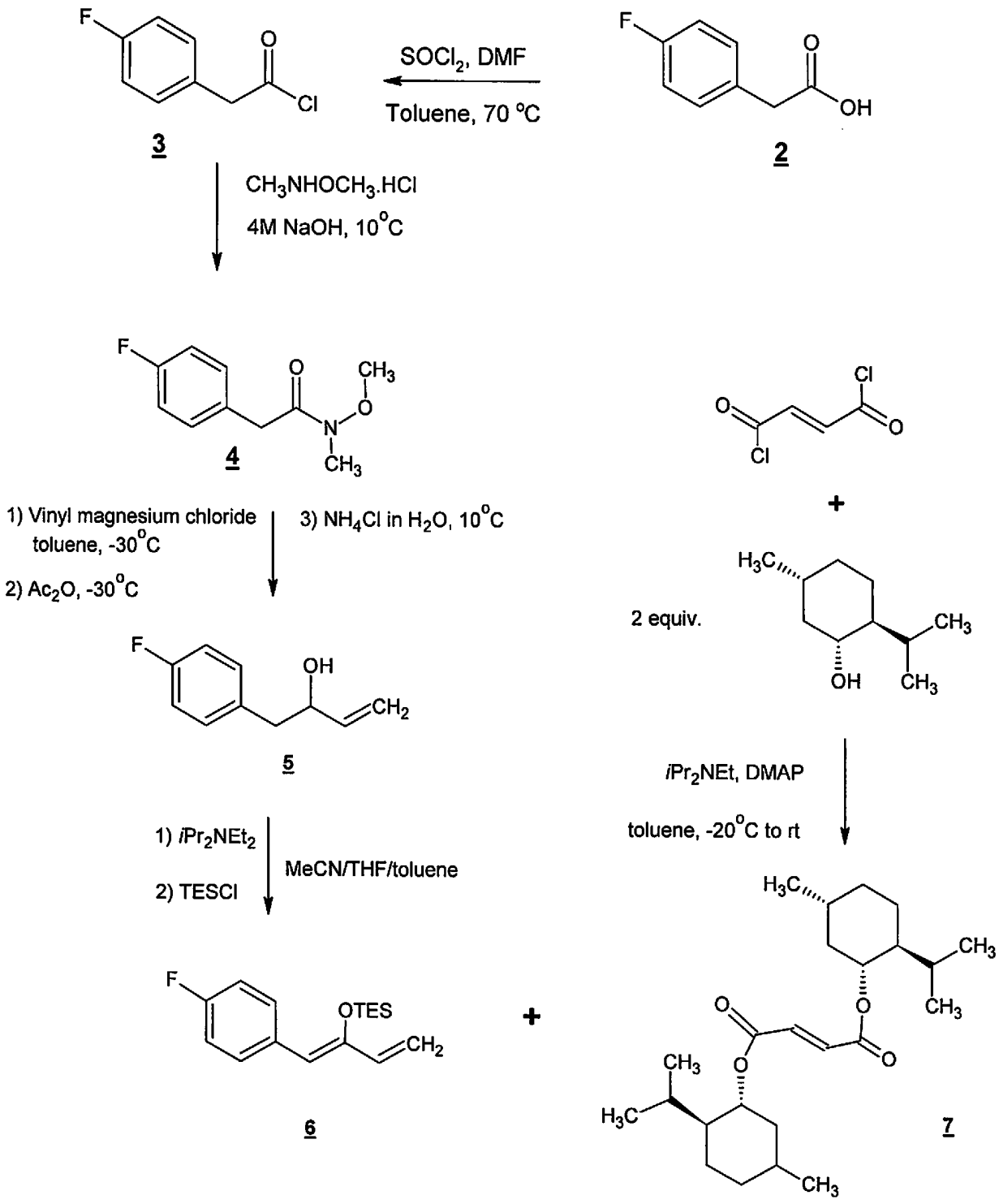

F
O
Cl
3
SOCl2, DMF
Toluene, 70 °C
F
O
OH
2
CH3NHOCH3.HCl
4M NaOH, 10°C
F
O
CH3
N
O
CH3
4
1) Vinyl magnesium chloride
toluene, -30°C
2) Ac2O, -30°C
3) NH4Cl in H2O, 10°C
F
OH
CH2
5
1) iPr2NEt2
2) TESCl
MeCN/THF/toluene
F
OTES
CH2
6
+
Cl
O
O
Cl
+
2 equiv.
H3C
CH3
OH
CH3
iPr2NEt, DMAP
toluene, -20°C to rt
H3C
CH3
CH3
O
O
O
O
CH3
H3C
O
CH3
7

FIG. 1 (cont.)

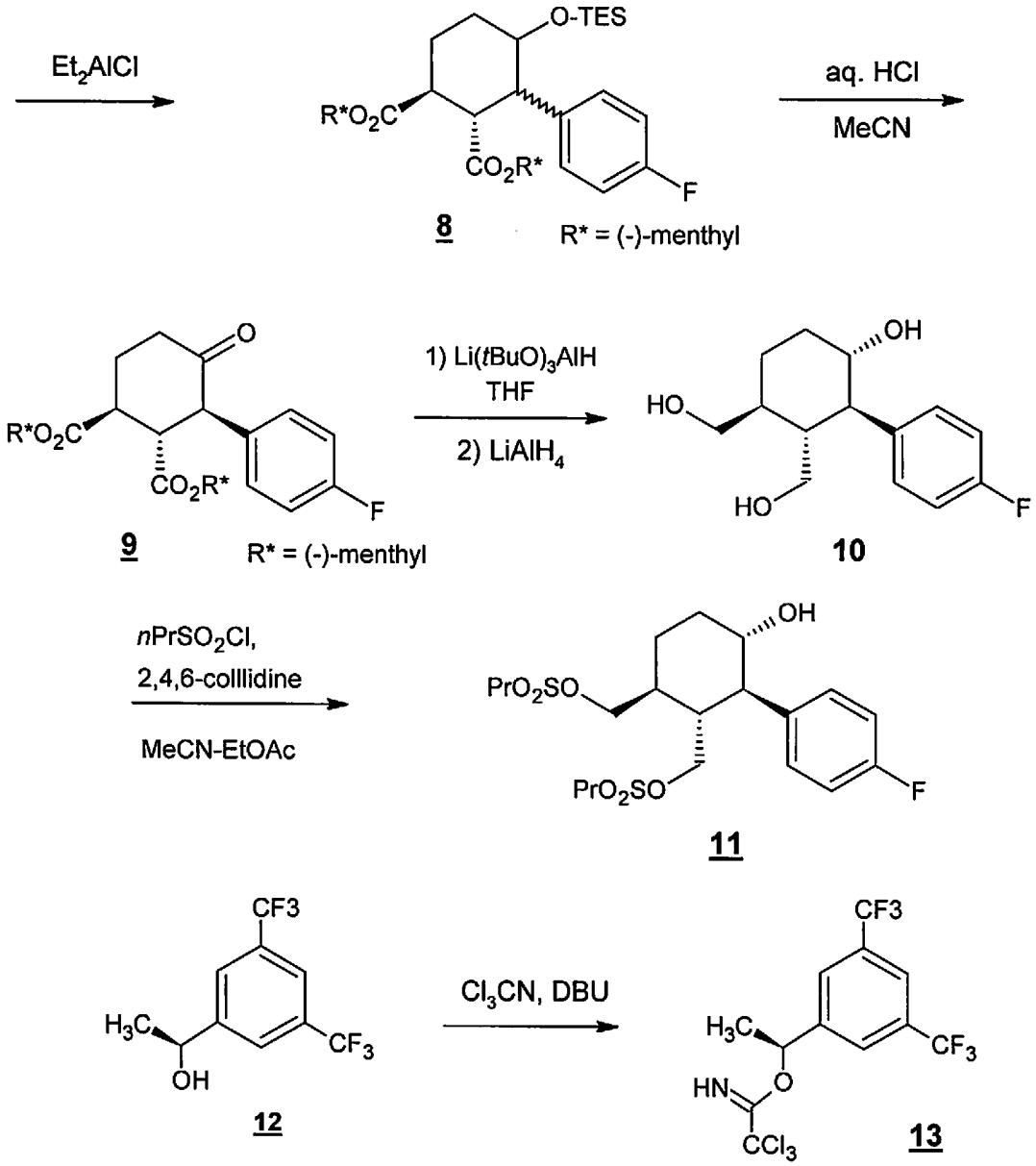

Et2AlCl
O-TES
R*O2C
CO2R*
F
8
R* = (-)-menthyl
aq. HCl
MeCN
O
R*O2C
CO2R*
F
9
R* = (-)-menthyl
1) Li(tBuO)3AlH
THF
2) LiAlH4
OH
HO
HO
F
10
nPrSO2Cl,
2,4,6-collidine
MeCN-EtOAc
OH
PrO2SO
PrO2SO
F
11
CF3
H3C
CF3
OH
12
Cl3CN, DBU
CF3
H3C
CF3
HN
O
CCl3
13

FIG. 1 (cont)

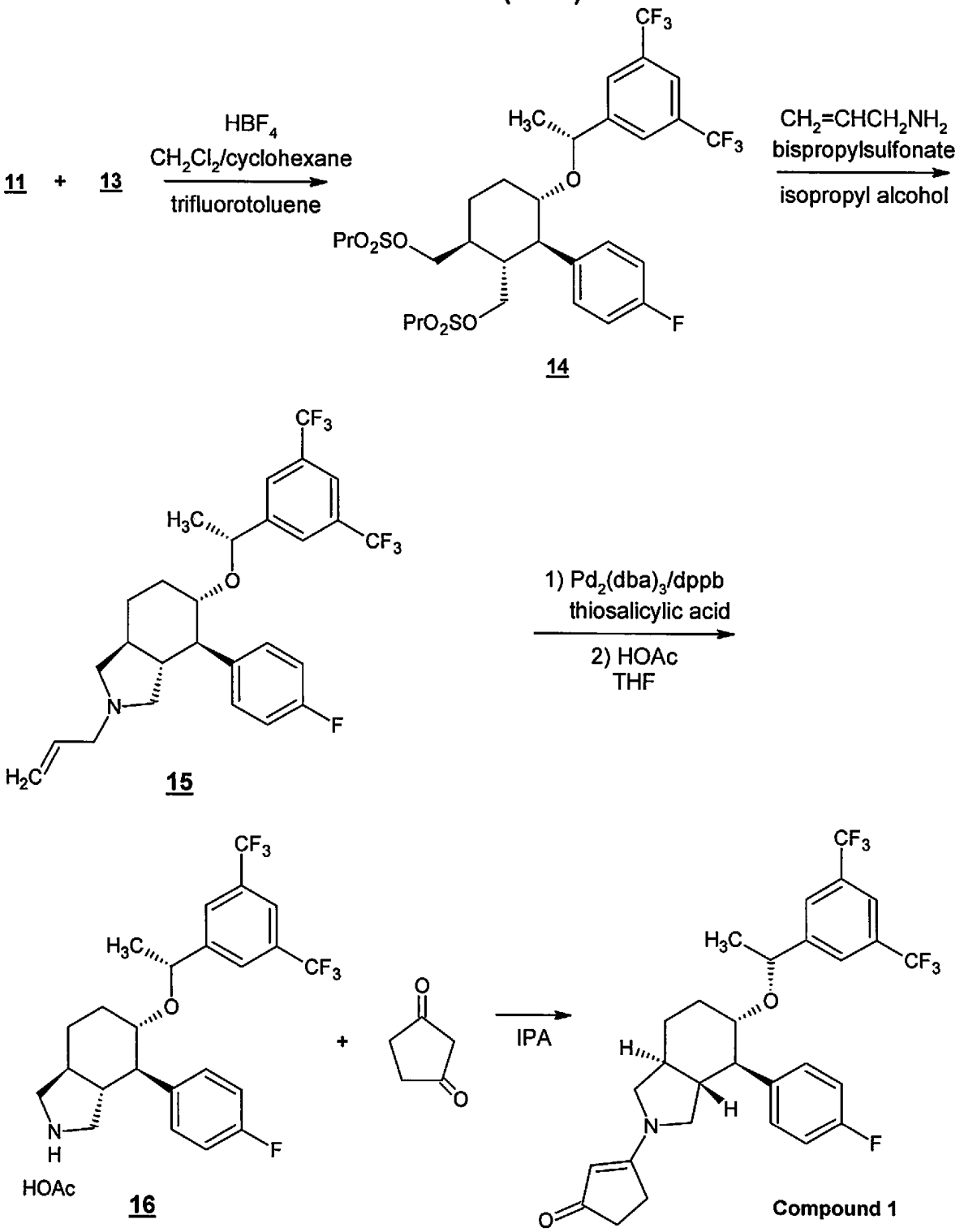

11 + 13
HBF4
CH2Cl2/cyclohexane
trifluorotoluene
CH2=CHCH2NH2
bispropylsulfonate
isopropyl alcohol
14
1) Pd2(dba)3/dppb
thiosalicylic acid
2) HOAc
THF
15
16
HOAc
IPA
Compound 1

FIG. 2

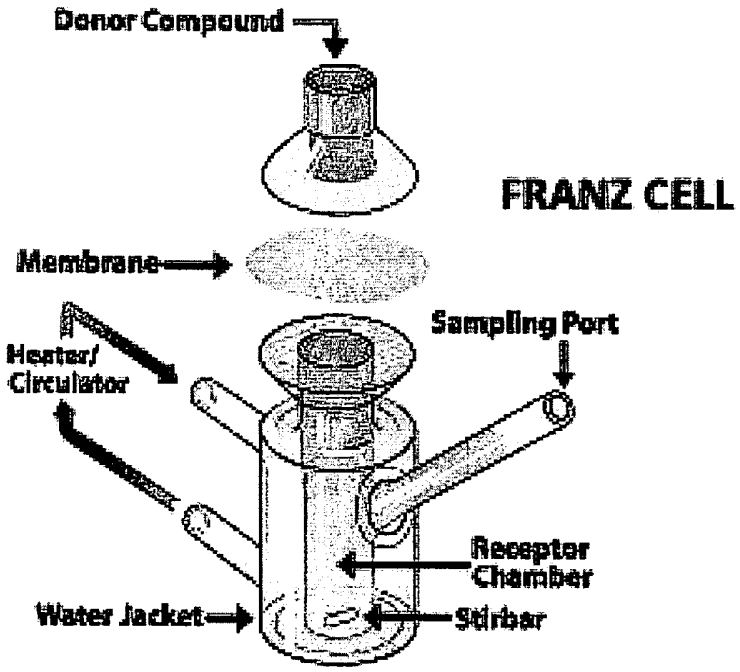

Donor Compound
FRANZ CELL
Membrane
Sampling Port
Heater/
Circulator
Receptor
Chamber
Water Jacket
Stirbar

FIG. 3

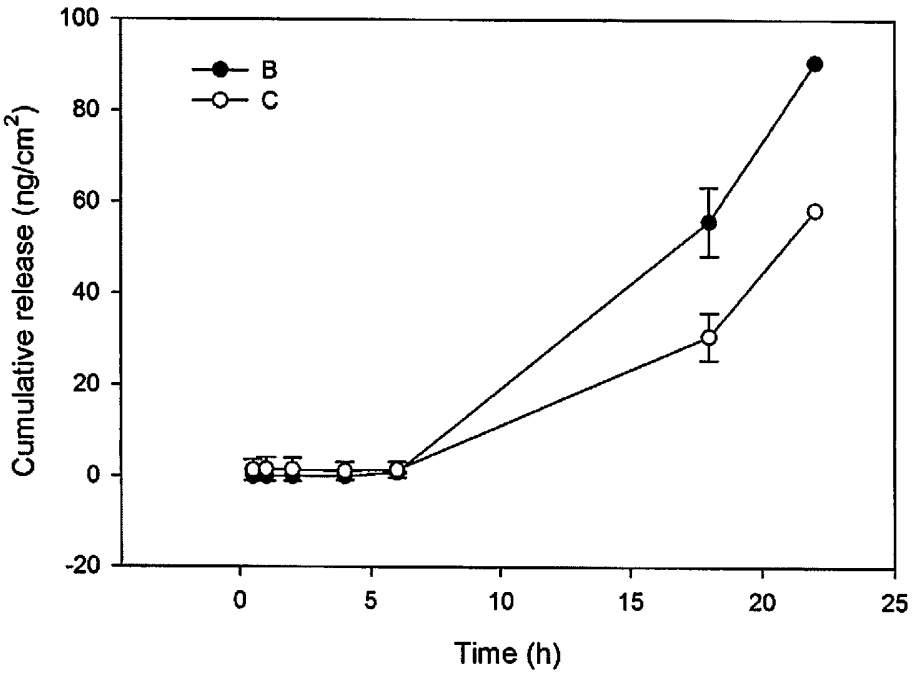
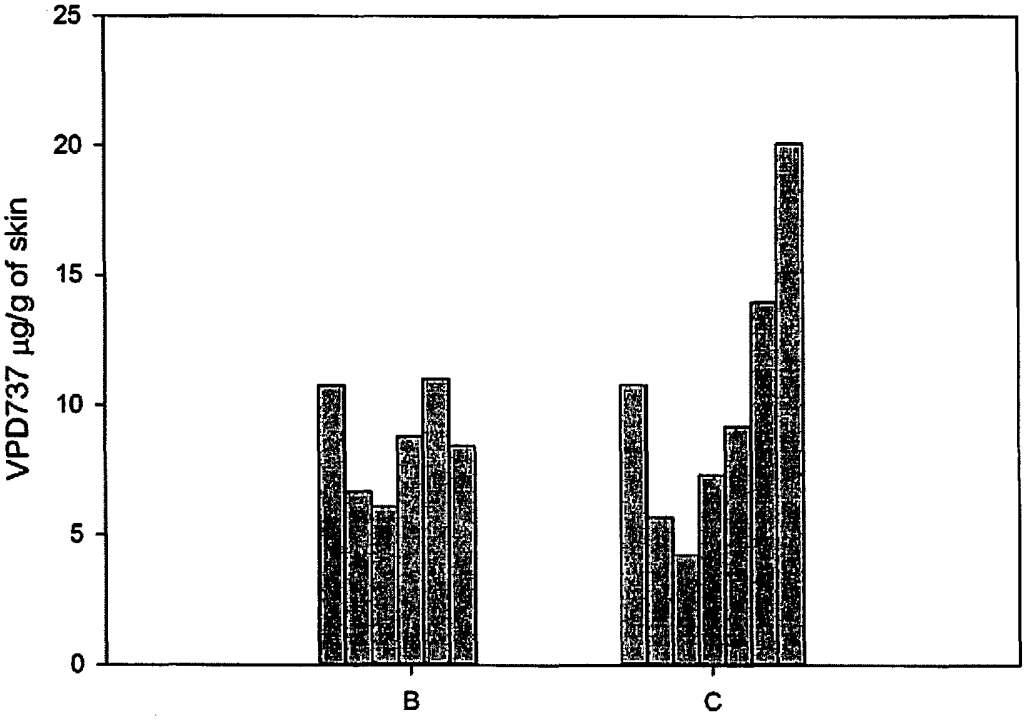

100
80
60
40
20
0
-20
B
C
Cumulative release (ng/cm2)
0
5
10
15
20
25
Time (h)

FIG. 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/043811

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/403 A61P17/04 A61P25/20
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/030389 A2 (MERCK & CO INC [US]; DOKOU ELENI [US]; FARRER BRIAN [US]; KEMP ERIC [U) 13 March 2008 (2008-03-13) claims ----- SONJA STÄNDER ET AL: "Targeting the Neurokinin Receptor 1 with Aprepitant: A Novel Antipruritic Strategy", PLOS ONE, vol. 5, no. 6, 1 January 2010 (2010-01-01) , pages e10968-e10968, XP055089771, ISSN: 1932-6203, DOI: 10.1371/journal.pone.0010968 cited in the application page 3 - page 4 ----- -/--	1-29
X		1-29

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2014	13/11/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Zimmer, Barbara

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/043811

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DANIELE SANTINI ET AL: "Aprepitant for management of severe pruritus related to biological cancer treatments: a pilot study", THE LANCET ONCOLOGY, vol. 13, no. 10, 18 September 2012 (2012-09-18), pages 1020-1024, XP055089772, ISSN: 1470-2045, DOI: 10.1016/S1470-2045(12)70373-X page 1021	1-29
X	TSUYOSHI OHMURA ET AL: "Involvement of substance P in scratching behaviour in an atopic dermatitis model", EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 491, no. 2-3, 1 May 2004 (2004-05-01), pages 191-194, XP055138410, ISSN: 0014-2999, DOI: 10.1016/j.ejphar.2004.03.047 page 194	1-29
X	X. ZHANG ET AL: "Activation of Neurokinin-1 Receptors Increases the Excitability of Guinea Pig Dorsal Root Ganglion Cells", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 343, no. 1, 26 June 2012 (2012-06-26), pages 44-52, XP055138411, DOI: 10.1124/jpet.112.196113 page 51	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/043811

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-29

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-29

Serlopitant for use in the treatment of pruritus

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2. claims: 30, 31

Serlopitant for use in aiding sleep

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/043811

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008030389 A2	13-03-2008	AU 2007293393 A1	13-03-2008
		CA 2662435 A1	13-03-2008
		EP 2063885 A2	03-06-2009
		JP 2010502703 A	28-01-2010
		US 2010209496 A1	19-08-2010
		WO 2008030389 A2	13-03-2008

(19)中华人民共和国国家知识产权局

(12)发明专利申请

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PCT/US2014/043811 2014.06.24

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(74)专利代理机构 中国专利代理(香港)有限公司 72001
代理人 李唐 黄希贵

(51)Int.Cl.
A61K 31/403(2006.01)
A61P 17/04(2006.01)
A61P 25/20(2006.01)

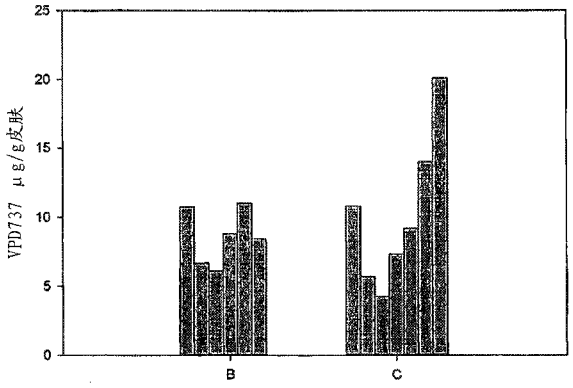
权利要求书2页 说明书37页 附图5页

(54)发明名称

NK-1受体拮抗剂司洛匹坦在瘙痒中的用途

(57)摘要

本发明涉及使用NK-1受体拮抗剂(如司洛匹坦)治疗瘙痒的方法。本发明还涉及包含NK-1受体拮抗剂(如司洛匹坦)的药物组合物。此外,本发明涵盖使用司洛匹坦及另外的止痒剂来治疗瘙痒相关病况,及司洛匹坦作为安眠药(任选地与另外的睡眠辅助药剂组合)的用途。



CN 105473138 A

1.治疗有此类治疗需求的患者中的瘙痒的方法，其包括向所述患者施用治疗有效量的3-[(3aR,4R,5S,7aS)-5-[(1R)-1-[3,5-双(三氟甲基)苯基]乙氧基]-4-(4-氟苯基)-1,3,3a,4,5,6,7,7a-八氢异吲哚-2-基]环戊-2-烯-1-酮(司洛匹坦)或其药学上可接受的盐、溶剂合物或多晶型物。

2.根据权利要求1的方法，其中所述治疗有效量包含一天一次或多次0.10mg、0.15mg、0.20mg、0.25mg、0.5mg、0.75mg、1mg、2mg、2.5mg、3mg、4mg、5mg、6mg、7mg、8mg、9mg、10mg、15mg、20mg、25mg或30mg的剂量。

3.根据权利要求2的方法，其中所述治疗有效量包含一天一次0.25mg、1mg或5mg的剂量。

4.根据权利要求1的方法，其中所述治疗有效量包含约0.1mg至约30mg或约1mg至约7.5mg的剂量。

5.根据权利要求1的方法，其中所述治疗有效量以片剂的形式口服施用。

6.根据权利要求1的方法，其中一天一次于睡前施用所述治疗有效量。

7.根据权利要求1的方法，其中所述治疗有效量一天一次、隔天一次、三天一次、四天一次或一周一次施用。

8.治疗瘙痒的方法，所述方法包括根据时间表向有此类治疗需求的患者施用3-[(3aR,4R,5S,7aS)-5-[(1R)-1-[3,5-双(三氟甲基)苯基]乙氧基]-4-(4-氟苯基)-1,3,3a,4,5,6,7,7a-八氢异吲哚-2-基]环戊-2-烯-1-酮(司洛匹坦)或其药学上可接受的盐、溶剂合物或多晶型物，所述时间表包括：

a)首先施用至少一个负荷剂量；和

b)其次施用至少一个治疗有效的维持剂量。

9.根据权利要求8的方法，其中所述负荷剂量为所述维持剂量的五倍、四倍、三倍或两倍。

10.根据权利要求9的方法，其中所述负荷剂量为所述维持剂量的三倍。

11.根据权利要求8的方法，其中在第1天施用所述负荷剂量并在第2天及之后施用所述维持剂量。

12.根据权利要求8的方法，其中在睡前施用所述负荷剂量与所述维持剂量。

13.根据权利要求8的方法，其还包括在施用所述维持剂量前施用第二负荷剂量。

14.根据权利要求13的方法，其中所述负荷剂量为所述维持剂量的三倍，而所述第二负荷剂量为所述维持剂量的两倍。

15.根据权利要求8的方法，其中所述治疗有效的维持剂量为一天一次或多次施用的0.10mg、0.15mg、0.20mg、0.25mg、0.5mg、0.75mg、1mg、2mg、2.5mg、3mg、4mg、5mg、6mg、7mg、8mg、9mg、10mg、15mg、20mg、25mg或30mg。

16.根据权利要求15的方法，其中所述治疗有效的维持剂量包含一天一次施用的0.25mg、1mg或5mg的剂量。

17.根据权利要求8的方法，其中所述治疗有效的维持剂量包含约0.1mg至约30mg或约1mg至约7.5mg的剂量。

18.根据权利要求8的方法，其中所述治疗有效的维持剂量一天一次、隔天一次、三天一次、四天一次或一周一次施用。

19.根据权利要求8的方法，其中口服施用司洛匹坦。

20.根据权利要求1或8的方法，其中在至少两周的时期上施用治疗有效量或治疗有效的维持剂量的司洛匹坦。

21.根据权利要求1或8的方法，其中所述瘙痒与痒疹、遗传病或肝脏疾病相关。

22.根据权利要求21的方法，其中所述痒疹为结节性痒疹，所述遗传病为大疱性表皮松解症，且所述肝脏疾病为肝衰竭。

23.根据权利要求1或8的方法，其中局部施用司洛匹坦。

24.根据权利要求23的方法，其中皮肤或经皮施用司洛匹坦。

25.根据权利要求1或8的方法，其还包括施用一种或多种另外的止痒剂。

26.根据权利要求25的方法，其中所述一种或多种另外的止痒剂选自抗组胺剂、皮质类固醇、免疫调节剂、免疫抑制剂、抗抑郁药和抗惊厥药。

27.根据权利要求26的方法，其中：

所述抗组胺剂为无镇静作用的第二代和第三代抗组胺剂，如阿伐斯汀、阿司咪唑、氮卓斯汀、贝他斯汀、比拉斯汀、西替利嗪、左西替利嗪、依巴斯汀、非索非那定、酮替芬、左卡巴斯汀、氯雷他定、地氯雷他定、咪唑斯汀、奥洛他定、奎非那定、卢帕他定和特非那定；

所述皮质类固醇为具有适中或中等功效的皮质类固醇，如安西缩松0.1％(例如，霜剂)、二丙酸倍他米松0.05％(例如，Diprosone®霜剂/软膏)、戊酸倍他米松0.1％(例如，霜剂/软膏)、丁酸氯倍他松0.05％(例如，Eumovate®霜剂)、地奈德0.05％(例如，Tridesilon®霜剂/软膏和DesOwen®霜剂/软膏)、氟轻松0.01-0.2％(例如，Synalar®霜剂/软膏和Synemol®霜剂)、氟氢缩松0.05％(例如，Cordran®条带)、丙酸氟替卡松0.005％(例如，Cutivate®软膏)、丙酸氟替卡松0.05％(例如，Cutivate®霜剂)、卤米松0.05％(例如，霜剂)、丁酸氢化可的松0.1％(例如，Locoid®霜剂/软膏)、戊酸氢化可的松0.2％(例如，Westcort®霜剂/软膏)、糠酸莫米松0.1％(例如，Elocon®霜剂/软膏)、曲安奈德0.025-0.5％(例如，Aristocort®霜剂/软膏、Kenacomb®霜剂/软膏、Kenalog®霜剂和Viaderm®KC霜剂/软膏)和双乙酸呋曲安奈德0.5％(例如，霜剂/软膏)；

所述免疫调节剂和免疫抑制剂选自抗代谢药(例如，甲氨蝶呤)和钙依赖磷酸酶抑制剂(例如，环孢菌素、吡美莫司和他克莫司)；

所述抗抑郁药为5-羟色胺去甲肾上腺素再摄取抑制剂，如比西发定、度洛西汀、米那普仑、左旋米那普仑、西布曲明、文拉法辛和去甲文拉法辛；并且

所述抗惊厥药选自卡马西平、加巴喷丁、普瑞巴林和丙戊酸及其盐类(如丙戊酸钠)。

28.根据权利要求25至27中任一项的方法，其中局部施用所述一种或多种另外的止痒剂。

29.根据权利要求28的方法，其中皮肤或经皮施用所述一种或多种另外的止痒剂。

30.帮助睡眠的方法，其包括向患有睡眠问题或障碍的主体施用有效量的司洛匹坦或其药学上可接受的盐、溶剂合物或多晶型物，以及任选地，另外的睡眠辅助药剂。

31.根据权利要求30的方法，其中口服、颊面或舌下施用司洛匹坦与所述任选的另外的睡眠辅助药剂。

NK-1受体拮抗剂司洛匹坦在瘙痒中的用途

相关申请的交叉引用

[0001] 本申请要求均提交于2013年6月24日的美国专利申请号13/925,509和美国临时专利申请号61/838,784的优先权与权益。

技术领域

[0002] 本发明涉及采用NK-1受体拮抗剂治疗急性或慢性瘙痒的方法。本发明还涉及包含NK-1受体拮抗剂的药物组合物。

发明背景

[0003] 瘙痒(pruritus)或瘙痒(itch),是一种引起抓挠欲望的不舒服的皮肤感觉。尽管瘙痒可以是急性的,例如,由于昆虫叮咬,但是慢性瘙痒可由许多不同原因引起。这是一种与慢性疼痛相当的、使人严重虚弱的病况,其负面影响生活质量。

[0004] 慢性瘙痒困扰着全世界数以百万的人,然而确凿的流行病学数据非常有限。例如,一项研究报道了8-10%的奥斯陆(Oslo)人群患有由各种原因引发的慢性瘙痒(F.Dalgard等人,J.Investig.Dermatol.Symp.Proc.,2004,9(2):120-5)。患有某种疾病和病况的患者报道高慢性瘙痒发病率,包括患有银屑病(78-84%)、霍奇金病(25-35%)、透析患者(22%)和真性红细胞增多症(48%)的那些(M.Metz与S.Ständer,CME Dermatol.,2008;3(3):124-143)。慢性瘙痒还是皮肤T细胞淋巴瘤(68-93%)中的普遍症状,皮肤T细胞淋巴瘤是包括蕈样肉芽肿和Sézary综合征的疾病(N.Meyer等人,Acta Derm.Venereol.,2010,90:12-17)。瘙痒是老年病患中最常见的有关皮肤病的不适(S.Beauregard与B.A.Gilchrest,Arch.Dermatol.,1987,123:1638-43)。瘙痒常常是某些药物(如EGF受体拮抗剂)的副作用。

[0005] 抗组胺剂有时可以有效地治疗由急性荨麻疹引起的瘙痒,但许多慢性瘙痒疾病对常规的H1受体拮抗剂反应不佳(Tey H.L.与G.Yosipovitch;Br.J.Dermatol.,2011,165(1):5-17)。除微乎其微的功效外,抗组胺剂还可引起难以忍受的困倦。其它现有的疗法具有各式各样的缺陷。例如,抗惊厥药(如加巴喷丁(gabapentin))抑制瘙痒感知的脊髓机制,但其用途由于其起效慢(5-6周)而受限(Metz与Ständer,2008)。阿片受体拮抗剂(如纳络酮(naloxone)、纳美芬(nalmefene)和纳曲酮(naltrexone))可减轻肝病与肾病患者的瘙痒症状,但会产生显著的中枢神经和胃肠副作用(Metz与Ständer,2008;N.V.Bergasa等人,Hepatology,2006,44(5):1317-23)。

[0006] P物质(神经激肽-1(NK-1)受体的内源性配体)是瘙痒的重要中介物(T.Andoh等人,J.Pharmacol.Exp.Ther.,1998,286:1140-5)。皮内注射P物质引起人主体的瘙痒感觉,并引起小鼠的相关瘙痒反应。小鼠中P物质诱导的瘙痒相关反应不被抗组胺剂所抑制(B.Amatya等人,Skin Pharmacol.Physiol.,2010;23:133-138;C.Weidner等人,J.Invest.Dermatol.,2000,115:1015-1020)。在为研究P物质在瘙痒中的作用而设计的实验中,Ohmura等人报道了速激肽NK-1受体拮抗剂BIIF 1149 CL在NC/Nga小鼠的苦基氯诱导的皮炎模型中抑制了抓挠行为(Eur.J.Pharmacol.,2004,491:191 194;美国专利申请号2003/100565)。

[0007] 阿瑞吡坦(Emend®),一种NK-1受体拮抗剂,经FDA批准用于在化学疗法后预防化学诱导的恶心和吐(呕吐)。Duval与Dubertret首次报道了口服阿瑞吡坦(每日80mg)在治疗三名Sézary综合征患者的瘙痒时具有功效(N.Engl.J.Med.,2009,361(14):1415-6)。Torres等人披露了类似的结果(J.Am.Acad.Dermatol.,2012;66(1):e14-5)。Ständer等人进行了一项小规模的开放标签研究,其证明阿瑞吡坦显著地减轻了由诸如特应性素质与结节性痒疹的病况引起的慢性瘙痒。在此研究中,二十名此前无法治疗的患者在3至13天中被给与80mg的日剂量。百分之八十的患者感受到瘙痒强度有大幅降低(S.Ständer等人,PLoS One,2010,5:6,e10968)。然而,Wallengren在Ständer工作的基础上进行了后续的双盲研究,其将单剂量的以5%的浓度掺入亲脂性媒介物的局部阿瑞吡坦在患有各种病因的慢性瘙痒患者中测试。尽管该药物为皮肤所吸收,但是患者的瘙痒并未得到缓解(J.Wallengren,Arch.Dermatol.,2012,148(8):957-9)。

[0008] 尽管口服阿瑞吡坦通常是耐受良好的,但其极其昂贵,限制了其在慢性瘙痒中的用途(Tey,2011)。另外,阿瑞吡坦既是CYP3A4和CYP2C9的适度抑制剂,也是其诱导剂,预示着必须考虑到其与化学治疗剂以及皮质类固醇的药物-药物相互作用(Torres,2012)。Mir与Coriat已指出与阿瑞吡坦的药物-药物相互作用的风险很高,因为其可改变细胞色素P450 3A4同工型(CYP-3A4)的活性,这是一种涉及一系列常用处方药(包括酪氨酸激酶抑制剂)的代谢的酶,是诱导或是抑制CYP-3A4取决于同时给与哪几种药物。酪氨酸激酶抑制剂不诱导频繁的恶心和呕吐;因此,缺乏阿瑞吡坦与这些药物同时给药的临床经验。此外,酪氨酸激酶抑制剂的药代动力学在患者间波动很大,并且药物-药物相互作用是常见的(O.Mir与R.Coriat,The Lancet,2012,13:964-965)。因此,急性与慢性瘙痒需要另外的、安全的治疗。

发明概述

[0009] 在一个方面,本发明提供在有此类治疗需求的患者中治疗瘙痒的方法,包括向所述患者施用治疗有效量的3-[(3aR,4R,5S,7aS)-5-[(1R)-1-[3,5-双(三氟甲基)苯基]乙氧基]-4-(4-氟苯基)-1,3,3a,4,5,6,7,7a-八氢异吲哚-2-基]环戊-2-烯-1-酮或其药学上可接受的盐、溶剂合物或多晶型物。在一个实施方案中,所述治疗有效量包含一天一次或多次0.10mg、0.15mg、0.20mg、0.25mg、0.5mg、0.75mg、1mg、2mg、2.5mg、3mg、4mg、5mg、6mg、7mg、8mg、9mg、10mg、15mg、20mg、25mg或30mg的剂量。在另一个实施方案中,所述治疗有效量包含一天一次0.25mg、1mg或5mg的剂量。在还一个实施方案中,所述治疗有效量包含从约0.1mg至约30mg或从约1mg至约7.5mg的剂量。在另一个实施方案中,所述治疗有效量以片剂的形式口服施用。在还一个实施方案中,所述治疗有效量一天一次在睡前施用。在另一个实施方案中,所述治疗有效量一天一次、隔天一次、三天一次、四天一次或一周一次施用。在其它实施方案中,遵循长期给药方案施用司洛匹坦(serlopitant)。在一些实施方案中,在至少2周、3周、1个月、1.5个月、2个月、3个月、4个月、5个月、6个月或更长的时间段上施用治疗有效量的司洛匹坦。

[0010] 在另一方面,本发明提供治疗瘙痒的方法,由此根据时间表向有此类治疗需求的患者施用3-[(3aR,4R,5S,7aS)-5-[(1R)-1-[3,5-双(三氟甲基)苯基]乙氧基]-4-(4-氟苯基)-1,3,3a,4,5,6,7,7a-八氢异吲哚-2-基]环戊-2-烯-1-酮(司洛匹坦)或其药学上可接受的盐、溶剂合物或多晶型物,其中首先施用至少一个负荷剂量,并其次施用至少一个治疗

有效的维持剂量。在一个实施方案中，所述负荷剂量为所述维持剂量的五倍、四倍、三倍或两倍。在另一个实施方案中，所述负荷剂量为所述维持剂量的三倍。在还一个实施方案中，在第1天施用所述负荷剂量并在第2天及之后施用所述维持剂量。在另一个实施方案中，在睡前施用所述负荷剂量与所述维持剂量。在另一个实施方案中，所述方法还包括在施用所述维持剂量前施用第二负荷剂量。在一个实施方案中，所述负荷剂量为所述维持剂量的三倍，而所述第二负荷剂量为所述维持剂量的两倍。在还一个实施方案中，所述治疗有效的维持剂量为一天一次或多次施用的0.10mg、0.15mg、0.20mg、0.25mg、0.5mg、0.75mg、1mg、2mg、2.5mg、3mg、4mg、5mg、6mg、7mg、8mg、9mg、10mg、15mg、20mg、25mg或30mg。在另一个实施方案中，所述治疗有效的维持剂量包含一天一次施用的0.25mg、1mg或5mg的剂量。在还一个实施方案中，所述治疗有效的维持剂量包含从约0.1mg至约30mg或从约1mg至约7.5mg的剂量。在另一个实施方案中，所述治疗有效的维持剂量一天一次、隔天一次、三天一次、四天一次或一周一次施用。在其它实施方案中，遵循长期给药方案施用司洛匹坦(serlopitant)。在一些实施方案中，在至少2周、3周、1个月、1.5个月、2个月、3个月、4个月、5个月、6个月或更长的时间段上施用治疗有效的维持剂量的司洛匹坦。在某些实施方案中，口服施用司洛匹坦。

[0011] 在一个方面，本发明提供治疗瘙痒的药物组合物，其包含3-[(3aR,4R,5S,7aS)-5-[(1R)-1-[3,5-双(三氟甲基)苯基]乙氧基]-4-(4-氟苯基)-1,3,3a,4,5,6,7,7a-八氢异吲哚-2-基]环戊-2-烯-1-酮或其药学上可接受的盐、溶剂合物或多晶型物以及药学上可接受的载体。在一个实施方案中，所述药物组合物被配制成片剂，其包含化合物1或其药学上可接受的盐、溶剂合物或多晶型物以及一种或多种稀释剂、崩解剂、表面活性剂或润滑剂。在另一个实施方案中，所述组合物包括装满溶液的胶囊，所述溶液包含化合物1或其药学上可接受的盐、溶剂合物或多晶型物以及两亲剂。在还一个实施方案中，所述两亲剂为甘油、丙二醇或山梨醇的脂肪酸酯。在另一个实施方案中，所述药物组合物包含0.10mg、0.15mg、0.20mg、0.25mg、0.5mg、0.75mg、1mg、2mg、2.5mg、3mg、4mg、5mg、6mg、7mg、8mg、9mg、10mg、15mg、20mg、25mg或30mg的化合物1或其药学上可接受的盐、溶剂合物或多晶型物。在另一个实施方案中，所述组合物包含0.25mg、1mg或5mg的化合物1或其药学上可接受的盐、溶剂合物或多晶型物。

[0012] 在另一个方面，本发明提供在有此类治疗需求的患者中治疗急性或慢性瘙痒的方法，包括向所述患者施用治疗有效量的药物组合物，所述药物组合物包含3-[(3aR,4R,5S,7aS)-5-[(1R)-1-[3,5-双(三氟甲基)苯基]乙氧基]-4-(4-氟苯基)-1,3,3a,4,5,6,7,7a-八氢异吲哚-2-基]环戊-2-烯-1-酮或其药学上可接受的盐、溶剂合物或多晶型物以及药学上可接受的载体。在一个实施方案中，所述方法涉及采用被配制成片剂的药物组合物进行治疗，所述片剂包含化合物1或其药学上可接受的盐、溶剂合物或多晶型物以及一种或多种稀释剂、崩解剂、表面活性剂或润滑剂。在另一个实施方案中，所述方法涉及施用包括装满溶液的胶囊的组合物，所述溶液包含化合物1或其药学上可接受的盐、溶剂合物或多晶型物以及两亲剂。在还一个实施方案中，所述两亲剂为甘油、丙二醇或山梨醇的脂肪酸酯。在另一个实施方案中，所述方法涉及采用药物组合物进行治疗，所述药物组合物包含0.10mg、0.15mg、0.20mg、0.25mg、0.5mg、0.75mg、1mg、2mg、2.5mg、3mg、4mg、5mg、6mg、7mg、8mg、9mg、10mg、15mg、20mg、25mg或30mg的化合物1或其药学上可接受的盐、溶剂合物或多晶型物。在另一个实施方案中，所述组合物包含0.25mg、1mg或5mg的化合物1或其药学上可接受的盐、

溶剂合物或多晶型物。

[0013] 在还一个实施方案中，通过施用司洛匹坦(化合物1)与额外的止痒剂来治疗瘙痒相关的病况。在又还一个实施方案中，通过施用司洛匹坦(任选与额外的睡眠辅助药剂组合)来治疗睡眠问题或障碍。

[0014] 通过阅读以下说明书和权利要求书，本发明的其它目标对于本领域技术人员可能是显而易见的。

附图简述

[0015] 结合所附权利要求书中的特殊性阐明了本发明的新颖特征。通过参考以下示出了说明性实施方案(其中运用了本发明的原理)及其附图的详细描述，将获得对本发明的特征与优点更好的理解：

[0016] 图1描绘了司洛匹坦(化合物1)的合成方案。

[0017] 图2说明了用于体外研究药物皮肤渗透的Franz扩散池。

[0018] 图3示出了在皮肤渗透的体外研究中，司洛匹坦从局部制剂B和C进入到Franz扩散池的接收室于各个时间点的累积释放。

[0019] 图4示出了在Franz扩散池研究结束时保留在皮肤中的司洛匹坦(称为“VPD737”)的量。每根柱表示在250um皮肤层中，ug司洛匹坦/g皮肤。对于局部制剂B和C各自而言，所述柱从左到右表示保留在皮肤层(从角质层到真皮)中的司洛匹坦的量。

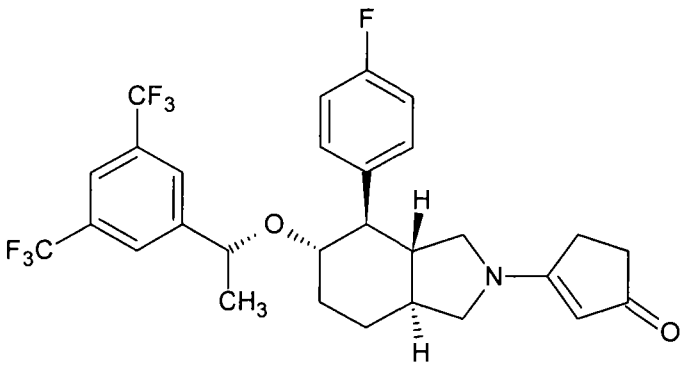
发明详述

[0020] 除非另行定义，否则本文中所用的全部技术与科学术语具有与本申请所属领域普通技术人员通常所理解的相同的含义。必须指出的是，如本文及所附权利要求书中所用，除非上下文另外明确规定，否则单数形式的“一个”、“一种”和“所述”包括复数指代物。

[0021] 现在将详细参照某些优选的治疗方法、化合物以及施用这些化合物的方法。本发明不限于那些优选的化合物和方法，而是被由此发布的权利要求所限定。

引言

[0022] 司洛匹坦(serlopitant)是一种神经激肽-1(NK-1)受体拮抗剂。本发明提供使用司洛匹坦或其药学上可接受的盐或水合物来治疗慢性瘙痒及相关病症的方法。在化学上，通用名司洛匹坦(serlopitant)是指化合物1的化合物：



化合物 1

该化合物的I.U.P.A.C.名称为3-[(3aR,4R,5S,7aS)-5-[(1R)-1-[3,5-双(三氟甲基)苯基]乙氧基]-4-(4-氟苯基)-1,3,3a,4,5,6,7,7a-八氢异吲哚-2-基]环戊-2-烯-1-酮。或者，化合物1可被命名为3-[(3aR,4R,5S,7aS)-5-{(1R)-1-[3,5-双(三氟甲基)苯基]乙氧基}-4-(4-氟苯基)八氢-2H-异吲哚-2-基]环戊-2-烯-1-酮。对于本发明的目的而言，应当

理解:化合物1的任何这些名称可以互换使用并具有相同含义。还应理解:本发明还涵盖司洛匹坦(化合物1)的外消旋形式。

[0023] 司洛匹坦此前已作为神经激肽-1(NK-1)受体拮抗剂被公开,其为速激肽特别是P物质的抑制剂(J.Jiang等人,J.Med.Chem.,2009,52:3039-3046)。神经激肽受体是G蛋白偶联受体大家族的一部分,它们通过激活磷酸肌醇信号转导途径来激发其许多效果。NK-1受体既存在于中枢与周围神经系统,也存在于血管内皮细胞、肌肉和免疫系统的细胞中。化合物1对克隆的人NK-1受体相较克隆的人NK-2和NK-3受体有异乎寻常的选择性(>39,000倍),正如使用稳定表达各个受体的中国仓鼠卵巢细胞所展示的(Jiang等人,2009)。Jiang等人证明司洛匹坦以46pM的K_d结合人NK-1受体,并且其以61pM的IC_{50}置换与相同受体结合的P物质。

[0024] 化合物1是人CYP-3A4、2C8、2C9、2C19、2D6及1A2酶的弱可逆抑制剂,其IC_{50}值分别为39、58、30、29、35及>100μM。司洛匹坦在人肝细胞的三个单独制备物中未显著诱导CYP-3A4 mRNA。这些数据表明司洛匹坦将在人体内具有最低的药物-药物相互作用倾向,并且相比其它NK-1受体拮抗剂,任何药物-药物相互作用将会减少。尽管在超过145项试验中对司洛匹坦的广泛反筛查识别出多个介于1至10μM的弱活性,但没有在试验中观察到IC_{50}<1μM。因此,脱靶活性相比hNK-1活性效力低了不止20000倍(Jiang等人,2009)。

[0025] 已指出,司洛匹坦及其类似物将可用于预防和治疗多种临床病况,所述病况通过过量的速激酶(特别是P物质)活性的存在来表征。司洛匹坦已被披露用于治疗呕吐及尿失禁(美国专利号:US 7,217,731、US 7,345,083、US 7,544,815、US 7,645,790和US 7,893,091,其公开内容通过引用并入本文;美国已公开申请号:US 2009/0270477、US 2010/0113469和US 2010/0209496,其公开内容通过引用并入本文;以及PCT公开:WO 2007/146224,其公开内容通过引用并入本文)。

[0026] 司洛匹坦的安全性和耐药性已在若干个用于治疗或预防膀胱过度活动症(OAB)的人临床试验中得到评价。在一项研究中,总共557名OAB患者被随机分配至这项双盲、安慰剂对照与活性对照(active-controlled)(托特罗定,tolterodine)的剂量范围研究。每日0.25与4mg司洛匹坦相比安慰剂显著减少每日排尿次数。不存在药物相关的严重不良体验,并且该药物整体上耐受性良好。然而,司洛匹坦未显示与排尿频率存在剂量效应关系,并且其未显著影响尿急、急迫性尿失禁和完全性尿失禁的次要有效终点。托特罗定在全部有效终点上均较司洛匹坦从数值上看更有效,并且其较安慰剂在统计上显著的更有效。司洛匹坦与接受托特罗定(一种毒蕈碱拮抗剂)的患者中常见的口干的不良体验不相关。(参见:Frenkl,T.L.等人,J.Urology,2009,181(4),Suppl.S,p.676;Frenkl,T.L.等人,Neurourol.Urodyn.,2009,28(2):143-144;Frenkl,T.L.等人,European Urology Supplements,2009,8(4):134;Frenkl,Tara L等人,J.Urology,2010,184(2):616-622.)。

司洛匹坦的化学描述

[0027] 术语"药学上可接受的盐"是指由药学上可接受的、无毒性的碱或酸(包括无机或有机碱以及无机或有机酸)制备的盐。源自无机碱的盐包括:铝盐、铵盐、钙盐、铜盐、铁盐、亚铁盐、锂盐、镁盐、锰盐、亚锰盐、钾盐、钠盐、锌盐等。特别优选的是铵盐、钙盐、镁盐、钾盐和钠盐。固体形式的盐可以不止一种晶体结构存在,并且还可以是水合物的形式。源自药学上可接受的有机无毒碱的盐包括伯胺、仲胺及叔胺、取代胺的盐,所述取代胺包括天然存在

的取代胺、环胺与碱性离子交换树脂，如精氨酸、甜菜碱、咖啡因、胆碱、N,N′-二苯基乙二胺、二乙胺、2-二乙氨基乙醇、2-二甲氨基乙醇、乙醇胺、乙二胺、N-乙基吗啉、N-乙基哌啶、葡糖胺、氨基葡萄糖、组氨酸、海巴、异丙胺、赖氨酸、甲基葡胺、吗啉、哌嗪、哌啶、聚胺树脂、普鲁卡因、嘌呤、可可碱、三乙胺、三甲胺、三丙胺、氨丁三醇等。当本发明的化合物为碱性时，可由药学上可接受的无毒酸(包括无机和有机酸)制备盐。这类酸包括：乙酸、苯磺酸、苯甲酸、樟脑磺酸、柠檬酸、甲磺酸、富马酸、葡糖酸、谷氨酸、氢溴酸、盐酸、羟乙磺酸、乳酸、马来酸、苹果酸、扁桃酸、甲磺酸、粘液酸、硝酸、扑酸、泛酸、磷酸、琥珀酸、硫酸、酒石酸、对甲苯磺酸等。特别优选的是柠檬酸、氢溴酸、盐酸、马来酸、磷酸、硫酸、富马酸和酒石酸。应当理解，如本文中所用，对本发明化合物的提及意在还包括药学上可接受的盐。

[0028] 术语“溶剂合物”是指由溶质离子或分子与一个或多个溶剂分子组成的聚集体。“溶剂合物”包括水合物，即，目标化合物与水的聚集体。应当理解，如本文中所用，对本发明化合物的提及意在还包括溶剂合物。

[0029] 术语“多晶型物”是指可以不同形式结晶的化合物的晶体形式。本发明还涵盖司洛匹坦的多晶型物。司洛匹坦的多晶型物的实例包括但不限于无基质(free base)司洛匹坦的无水晶体形式I和II，如公开于Kuethe等人的美国专利申请公开号2009/0270477。通过从对应于间距d为10.4、9.9、9.2、5.5、5.0、4.1、3.9、3.6和3.5埃的X射线粉末衍射图获得的衍射峰来表征形式I。通过从对应于间距d为7.7、5.3、4.9、4.8、4.6、4.2、3.9、3.8和2.8埃的X射线粉末衍射图获得的衍射峰来表征形式II。US 2009/0270477以其整体通过引用并入本文。

[0030] 化学合成可依照Jiang等人所述制备司洛匹坦(J.Med.Chem.2009,52:3039-3046)，其以其整体通过引用并入本文。或者，可采用Kuethe等人在美国专利号7,544,815中或Bunda等人在美国专利号7,217,731中所述的方法，其两者以其整体通过引用并入本文。

[0031] Kuethe等人的方法在图1中有述。简而言之，使市售4-氟苯乙酸(2)(Sigma-Aldrich Co.LLC,St.Louis,MO)与氯化亚砜在DMF/甲苯中反应以得到酰基氯(3)。然后使该酰基氯(3)与Weinreb胺的盐酸盐($CH_3NHOCH_3 \cdot HCl$)在存在氢氧化钠的情况下反应以得到2-(4-氟苯基)-N-甲氧基-N-甲基乙酰胺(4)。乙烯基格氏反应(Grignard reaction)将(4)转化成1-(4-氟苯基)丁-3-烯-2-酮(5)。由(5)与三乙基氯硅烷(TESCl)在存在iPr_2NEt_2的情况下反应来生成TES二烯基醚(dienyl ether)(6)。

[0032] 使市售富马酰氯与两当量的(-)-薄荷醇(均得自Sigma-Aldrich)反应以得到二-(-)-富马酸薄荷酯(7)。(6)和(7)之间的狄尔斯-阿尔德反应(Diels-Alder reaction)生成(8)。该二烯烃所存在的任何E-异构体都不参与狄尔斯-阿尔德反应。(8)在酸中的脱保护与差向异构化得到(9)。初始时，(8)的脱甲硅烷基作用得到2,3-顺-和2,3-反-酮的混合物，其由所需(9)的结晶所驱动，异构化为主要反式的化合物。使用三-叔丁氧基氢化铝锂($Li(t\text{-}BuO)_3AlH$)，然后是氢化铝锂($LiAlH_4$)来还原(9)，生成三醇(10)，然后将其用正丙基磺酰氯($nPrSO_2Cl_2$)保护以得到(11)。

[0033] 使S-BTBA((S)-1-[3,5-双(三氟甲基)]苯基乙醇))(12)与三氯乙腈(Sigma-Aldrich)在存在碱1,8-二氮杂双环十一碳-7-烯(DBU)的情况下反应以生成亚氨酸酯(imidate)(13)。采用HBF_4催化(11)与(13)的反应以得到醚(14)。用丙烯胺与磺酸二丙基酯(bis-propylsulfonate)处理将(14)环化成丙烯胺保护的吡咯烷(15)。使用硫代水杨酸和

1,4-双(二苯基膦基)丁烷(dppb),然后是双(二亚苄基丙酮)钯($Pd_2(dba)_3$)来移除烯丙基保护基团,并使用乙酸分离得到晶体(16)。最终,使(16)与1,3-环戊二酮(Sigma-Aldrich)在异丙醇中反应以得到化合物1。化合物1是一种白色至灰白色的粉末。其易溶于甲醇,可溶于乙醇,微溶于乙酸异丙酯,略溶于异丙醇、乙酸乙酯和乙腈,且不溶于水。

药物组合物

[0034] 含有司洛匹坦或其药学上可接受的盐、溶剂合物或多晶型物作为活性成分的组合物可有利地用于治疗慢性瘙痒。虽然司洛匹坦或其药学上可接受的盐、溶剂合物或多晶型物有可能被单独施用,但是优选地其作为制剂存在。所述组合物或剂型可以单独,或与其他药剂组合施用或应用。所述制剂还可与另一种药物活性剂组合来向患者递送司洛匹坦。

[0035] 本文中所用的术语"组合物"旨在涵盖包含预定量或比例的特定成分的产品,以及直接或间接得自特定量的所述特定成分的组合的任何产品。该与药物组合物有关的术语旨在涵盖包含一种或多种活性成份及任选的包含惰性成分的药学上可接受的载体的产品,以及直接或间接地,得自任何两种或多种所述成分的组合、复合或聚集,或得自一种或多种所述成分的解离,或得自一种或多种所述成分的其它类型的反应或相互作用的任何产品。通常,药物组合物的制备是通过采用液体载体或细分的固体载体或两者,使活性成分均匀并紧密地结合,然后,如有必要,使产品成形为所需制剂。在药物组合物中包含活性目标化合物,其量足以对疾病的过程或状况产生所需效果。因此,本发明的药物组合物涵盖通过使本发明的化合物与药学上可接受的载体混合而制得的任何组合物。分别根据常规的混合、造粒或包衣方法来制备所述组合物,并且其含有约0.1至75%、优选约1至50%的活性成分。

[0036] "药学上可接受的"意指载体、稀释剂或赋形剂必须与所述制剂的其它成分相容并且对其接受者无害。旨在用于口服的药物组合物可根据药物组合物制造领域已知的任何方法制备,并且此类组合物可含有一种或多种选自甜味剂、矫味剂、染色剂与防腐剂的试剂,从而得到药学上精制且可口的制剂。

[0037] 片剂包含与适用于片剂制造的、无毒药学上可接受的赋形剂混合的活性成分。这些赋形剂可以是,例如,惰性稀释剂如碳酸钙、碳酸钠、乳糖、磷酸钙或磷酸钠;造粒和崩解剂,例如,玉米淀粉或藻酸;结合剂,例如淀粉、明胶或阿拉伯树胶;以及润滑剂,例如硬脂酸镁、硬脂酸或滑石。所述片剂可以不包衣或其可以采用已知技术包衣以延缓在胃肠道中的崩解和吸收,并从而在更长的时间段上提供持续的作用。片剂可以通过将活性成分任选地与一种或多种药学上可接受的成分一起压制或模制而制得。压缩片剂的制备可通过在合适的机器中将呈自由流动形式(如粉末或颗粒)的活性成分(任选地与粘结剂、润滑剂、惰性稀释剂、表面活性剂或分散剂混合)压缩而成。模制片的制备可通过在合适的机器中,将经惰性液体稀释剂湿润的粉末化的活性成分与合适的载体的混合物模制而成。

[0038] 用于口服的组合物还可作为硬明胶胶囊呈现,其中使活性成分与惰性固体稀释剂(例如,碳酸钙、磷酸钙或高岭土)混合,或作为软明胶胶囊呈现,其中使活性成分与水或油介质(例如,花生油、液态石蜡或橄榄油)混合。具体来说,本发明的药物组合物可包括装满液体的胶囊剂型,其中活性成分以液体与半固体赋形剂的某些组合存在于溶液中。在一个实施方案中,本发明涉及包含活性剂3-[(3aR,4R,5S,7aS)-5-{(1R)-1-[3,5-双(三氟甲基)苯基]乙氧基}-4-(4-氟苯基)八氢-2H-异吲哚-2-基]环戊-2-烯-1-酮(化合物1)或其药学上可接受的盐、溶剂合物或多晶型物以及两亲剂的溶液,所述两亲剂为甘油、丙二醇或山梨

醇的脂肪酸酯，如美国已公开申请号2010/0209496中所述(Dakou等人)，该文献以其整体通过引用并入本文。优选地，所述两亲剂主要由C8至C12饱和脂肪酸的单甘油酯和双甘油酯及其混合物组成。

[0039] 用于口服施用的组合物还可被配制成含水悬浮液，其含有活性成分与适于制造含水悬浮液的赋形剂的混合物。可通过将活性成分悬浮于合适的油中来配制油悬浮液。也可采用水包油乳状液。适于通过添加水来制备含水悬浮液的可分散粉末和颗粒提供了活性成分与分散剂或润湿剂、悬浮剂以及一种或多种防腐剂的混合物。

[0040] 本发明的活性成分可以在口服持续释放制剂中施用。“持续释放”是指以一定速率从剂型中释放活性剂，所述速率能在相对于通过口服施用所述药剂的常规制剂所达到的延长的时间段上，有效地在全身血液循环中使所述药剂或其活性代谢物达到治疗量。在数小时的延长期上进行所述药剂的释放，例如，在至少6小时的时间段上、在至少8小时的时间段上、在至少12小时的时间段上或在至少24小时的时间段上。

[0041] 合适的局部制剂与剂型包括软膏、霜剂、凝胶、洗剂、糊剂等，如Remington:The Science and Practice of Pharmacy(21st Edition,University of the Sciences in Philadelphia,2005)中所述。软膏是通常基于矿脂或其它石油衍生物的半固体制剂。正如本领域技术人员将认识到的，所用的具体的软膏基质是将提供最佳的药物递送，并且优选地，还将提供其它所需的特性，例如，润肤等的软膏基质。霜剂为粘滞液体或半固体乳状液，水包油或油包水乳状液。霜剂基质是可水洗的，并且包含油相、乳化剂和水相。所述油相，也称为“内部”相，通常包含矿脂和脂肪醇如鲸蜡醇或硬脂醇。所述水相通常(但是未必)在体积上超过所述油相并且一般包含湿润剂。所述霜剂制剂中的乳化剂通常是非离子的、阴离子的、阳离子的或两性的表面活性剂。凝胶是半固体、悬浮式的系统。单相凝胶含有基本上均匀分布在载液中的有机大分子(聚合物)，所述载液通常为含水的，但也优选地包含醇(如乙醇或异丙醇)以及任选包含油。为了制备均匀凝胶，可加入分散剂如醇或甘油，或者可通过研磨、机械混合或搅动或其组合来分散胶凝剂。洗剂是无摩擦地应用于皮肤表面的制剂，并且通常是液体或半液体制剂，其中固体颗粒(包括活性剂)存在于水或醇基质中。洗剂通常是细分的固体的悬浮液，并且通常将包含悬浮剂以产生更好的分散性以及包含用于使活性剂局部化并与皮肤保持接触的化合物。糊剂是半固体剂型，其中活性剂悬浮于合适的基质中。取决于基质的本质，糊剂被划分为脂肪膏或由单相水凝胶制成的那些。

[0042] 在局部制剂中可包含本领域技术人员已知的各种添加剂。例如，溶剂(包括相对少量的醇)可用于溶解某些药物物质。其它任选的添加剂包括遮光剂、抗氧化剂、芳香剂、着色剂、胶凝剂、增稠剂、稳定剂、表面活性剂等。还可加入其它试剂，如抗微生物剂，以防止贮藏变质，即，抑制微生物(如酵母和霉菌)的生长。对于那些具有异常低的经皮肤或粘膜组织渗透率的药物而言，在制剂中包含渗透增强剂可能是有利的。所述制剂还可包含减轻刺激的添加剂以最小化或消除由所述药物、所述增强剂或所述剂型的其它组分所引起的皮肤刺激或皮肤损伤的可能性。所述制剂还可包含醚生理上可接受的赋形剂或其它微量添加剂，如芳香剂、染料、乳化剂、缓冲剂、冷却剂(例如薄荷醇)、抗生素、稳定剂等。在一些情况下，一种组分可起到不止一种作用。

[0043] 局部制剂中活性剂的浓度可以千差万别，并且取决于各种因素，包括所治疗的疾病或病症、活性剂的性质与活性、所需的效果、可能的不良反应、活性剂抵达其预期标靶的

能力和速度，以及在患者和医生的专门知识范围内的其他因素。所述制剂通常将包含接近约0.1重量％至50重量％的活性剂，优选约0.1重量％至5重量％的活性剂，最佳约5重量％至20重量％的活性剂。

[0044] 在一些实施方案中，司洛匹坦的局部剂型被配制成颊侧或舌下片剂或丸剂。颊侧或舌下片剂或丸剂的优点包括避免首过代谢以及绕过胃肠吸收。除治疗有效量的司洛匹坦以外，所述颊侧或舌下片剂或丸剂可以包含合适的赋形剂，包括但不限于填充剂与稀释剂的任何组合(例如，甘露醇和山梨醇)、结合剂(例如，碳酸钠)、润湿剂(例如，碳酸钠)、崩解剂(例如，交联聚维酮和交联羧甲基纤维素钠)、润滑剂(例如，二氧化硅[包括二氧化硅胶体]和硬脂酰醇富马酸钠)、稳定剂(例如，碳酸氢钠)、矫味剂(例如，薄荷味)、甜味剂(例如，三氯蔗糖)以及染色剂(例如，氧化铁黄)。所述包含司洛匹坦的颊侧或舌下片剂或丸剂可用于治疗，例如，本文所述的任何与瘙痒相关的病症。

[0045] 本发明的药物组合物可被配制成储库(depot)制剂用于通过肌内注射或皮下注射施用。储库制剂是活性成分的有效的、耐受性良好的、持续或延缓释放的组合物，其在数周内都是治疗有效的，如至少一周、至少两周、至少三周、至少四周、至少五周或至少六周或更长。除所述活性剂外，另外的成分可用于本发明的储库制剂中，包括表面活性剂、增溶剂、乳化剂、防腐剂、等渗剂、分散剂、润湿剂、填充剂、溶剂、缓冲剂、稳定剂、润滑剂以及增稠剂。也可使用另外成分的组合。储库制剂中活性成分的量将取决于所治疗的瘙痒的严重程度。

[0046] 本发明的组合物可以单位剂型提供，并且可通过制药领域熟知的任何方法制备。术语“单位剂型”是指单个剂量，其中所有的活性与非活性成分被结合在合适的系统内，使得患者或给患者施用药物的人可以打开其中装有整个剂量的单个容器或包装，并且不需要将两个或更多个容器或包装中的任何组分混合到一起。单位剂型的典型实例是用于口服施用的片剂或胶囊。单位剂型的这些实例并非旨在以任何方式进行限制，而仅仅代表制药领域中单位剂型的典型实例。

[0047] 本发明的组合物还可作为试剂盒呈现，由此提供两种或更多种组分(可以是活性或非活性成分、载体、稀释剂等)以及指导患者或给患者施用药物的人制备实际剂型的说明书。此类试剂盒可提供有所有必要的材料及其所含的成分，或者其可包含使用或制造必须由患者或给患者施用药物的人独立获取的材料或组分的说明书。

包含司洛匹坦的局部组合物

[0048] 应用于皮肤或粘膜的局部制剂可用于治疗上皮肤或粘膜层的病况，并且可用于将活性剂经皮或经粘膜施用到皮肤或粘膜下的局部组织以及(如果需要)进入血液参与全身分配。局部施用的优点可包括：避免首过代谢、绕过胃肠吸收、递送具有相对较短的生物半衰期的活性剂、更可控地释放活性剂、以更均匀的血浆剂量施用活性剂以及改善使用者的依从性。

[0049] 通常，除本文别处所述的局部制剂的公开内容以外，适于局部施用的组合物包括但不限于：液体或半液体制剂(如喷雾、凝胶、擦剂、洗剂)、水包油或油包水乳状液(如霜剂、泡沫、软膏和糊剂)以及溶液或悬浮液如滴剂(例如，滴眼液、滴鼻液和滴耳液)。在一些实施方案中，局部组合物包含溶解、分散或悬浮于载体中的活性剂。所述载体可以为以下形式，例如，溶液、悬浮液、乳状液、软膏或凝胶基质，并可包含，例如，矿脂、羊毛脂、蜡(例如，蜂蜡)、矿物油、长链醇、聚乙二醇或聚乙二醇、稀释剂(例如，水和/或醇[例如，乙醇或丙二

醇])、乳化剂、稳定剂或增稠剂或其组合。局部组合物可包括，或局部制剂可经由其施用，例如，透皮贴剂、微针贴剂或离子电渗装置。透皮贴剂可包括，例如，由合适材料(例如，硝酸纤维素或醋酸纤维素、丙烯或聚碳酸酯)制成的微孔膜、皮肤粘合剂和衬底材料。局部组合物可以通过浓度梯度或主动机制(例如，电离层)经皮(包括穿过皮肤和经粘膜)递送活性剂。

[0050] 以下出于说明目的而描述了局部组合物代表性的种类。

I.包含渗透增强剂的局部组合物

[0051] 在一些实施方案中，局部组合物包含司洛匹坦和渗透增强剂。所述组合物可任选地包含额外的治疗剂。在某些实施方案中，所述组合物包含无基质形式的司洛匹坦。

[0052] 所述渗透增强剂增加皮肤或粘膜对所述治疗剂的渗透性。在某些实施方案中，所述渗透增强剂为N-月桂酰肌氨酸、辛基硫酸钠、月桂酸甲酯、肉豆蔻酸异丙酯、油酸、油酸甘油酯或月桂醇磺基醋酸钠或其组合。在某些实施方案中，所述组合物包含按重量/体积(w/v)计，约1-20％、1-15％、1-10％或1-5％的量的所述渗透增强剂。为进一步增强所述治疗剂穿透皮肤或粘膜的能力，所述组合物还可以包含表面活性剂、氮酮类化合物、醇、脂肪酸或酯或脂族硫醇。

[0053] 所述组合物还可包含一种或多种额外的赋形剂。合适的赋形剂包括但不限于：增溶剂(例如，C_2-C_8醇)、湿润剂或保湿剂(例如，甘油[甘油]、丙二醇、氨基酸及其衍生物、聚氨基酸及其衍生物以及吡咯烷酮羧酸及其盐及其衍生物)、表面活性剂(例如，月桂醇硫酸钠和去水山梨糖醇月桂酸酯)、乳化剂(例如，鲸蜡醇和硬脂醇)、增稠剂(例如，甲基纤维素、乙基纤维素、羟甲基纤维素、羟丙基纤维素、聚乙烯吡咯烷酮、聚乙烯醇和丙烯酸聚合物)以及制剂基质或载体(例如，聚乙二醇作为软膏基质)。作为非限制性实例，所述组合物的基质或载体可包含乙醇、丙二醇和聚乙二醇(例如，PEG300)以及任选的水性液体(例如，等渗磷酸盐缓冲盐水)。

[0054] 所述局部组合物可具有任何合适的剂型，如溶液(例如，滴眼液、滴鼻液或滴耳液)、悬浮液、乳液、霜剂、洗剂、凝胶、软膏、糊剂、果冻、泡沫、洗发水或喷雾。在一些实施方案中，将所述组合物应用于皮肤或粘膜，覆盖约10-800cm^2、10-400cm^2或10-200cm^2的表面积。所述组合物可将所述治疗剂递送到皮肤或粘膜或下面的组织。所述组合物还可被配制成用于所述治疗剂对全身循环的经皮给药，例如，作为透皮贴剂或微针贴剂。

II.包含渗透增强剂和挥发性液体的局部组合物

[0055] 在另外的实施方案中，局部组合物包含司洛匹坦、渗透增强剂和挥发性液体。所述组合物可任选地包含额外的治疗剂。在某些实施方案中，所述组合物包含无基质形式的司洛匹坦。

[0056] 所述渗透增强剂增加皮肤或粘膜对所述治疗剂的渗透性。在一些实施方案中，所述渗透增强剂选自：C_8-C_{18}烷基氨基苯甲酸酯(例如，C_8-C_{18}烷基对氨基苯甲酸酯)、C_8-C_{18}烷基二甲基氨基苯甲酸酯(例如，C_8-C_{18}烷基对二甲基氨基苯甲酸酯)、C_8-C_{18}烷基肉桂酸酯、C_8-C_{18}烷基甲氧基肉桂酸酯(例如，C_8-C_{18}烷基对甲氧基肉桂酸酯)和C_8-C_{18}烷基水杨酸酯。在某些实施方案中，所述渗透增强剂为水杨酸辛酯、对二甲基氨基苯甲酸辛酯或对甲氧基肉桂酸辛酯或其组合。

[0057] 所述挥发性液体可以是任何挥发性的、皮肤或粘膜耐受的溶剂。在某些实施方案中，所述挥发性液体为C_2-C_5醇或其水溶液，如乙醇或异丙醇或其水溶液。气溶胶推进剂(例

如，二甲醚)可被看作是挥发性液体。在一些实施方案中，所述挥发性液体用作所述组合物的载体或媒介物。

[0058] 所述组合物可任选地包含增稠剂。增稠剂的非限制性实例包括：纤维素类增稠剂(例如，乙基纤维素、羟丙基纤维素和羟丙基甲基纤维素)、聚维酮、聚丙烯酸/聚丙烯酸酯(例如，Carbopol®聚合物)、Sepigel®(聚丙烯酰胺/异链烷烃/月桂基聚氧乙烯醚-7)和Gantrez®系列聚甲基乙烯基醚/马来酸酐共聚物(例如，PMV/MA共聚物Gantrez®A-425的丁酯)。

[0059] 在一些实施方案中，所述组合物包含按重量计约0.5-10％、0.5-5％或1-5％的司洛匹坦、约1-20％、1-15％或1-10％的所述渗透增强剂和约40-98％、45-95％、50-90％或60-80％的所述挥发性液体。在另外的实施方案中，所述组合物任选地包含按重量计约1-40％、1-30％、1-20％或5-20％的水和/或约0.1-15％、0.5-10％或1-5％的增稠剂。

[0060] 出于说明的目的，在某些实施方案中，局部喷雾组合物包含约0.5-5％w/v的司洛匹坦、约2-10％w/v的水杨酸辛酯或对甲氧基肉桂酸辛酯和约95％的作为载体的乙醇水溶液。在另外的实施方案中，局部凝胶组合物包含约0.5-5％w/v的司洛匹坦、约1-10％w/v的水杨酸辛酯或对甲氧基肉桂酸辛酯、约0.5-5％w/v的Carbopol®聚丙烯酸和约70％的作为载体的乙醇水溶液，以及任选的约1-10％w/v的碱性溶液(例如，0.1N NaOH)。在另外的实施方案中，局部洗剂组合物包含约0.5-5％w/v的司洛匹坦、约1-10％w/v的水杨酸辛酯或对甲氧基肉桂酸辛酯、约1-5％w/v的乙基纤维素或羟丙基纤维素和约90％的作为载体的乙醇水溶液。

[0061] 所述组合物还可包含其它赋形剂，如复合剂(例如，石蜡油、有机硅油、植物油或脂肪酯如肉豆蔻酸异丙酯)、稀释剂、助溶剂(例如，丙酮或乙二醇醚如二乙二醇单乙醚)、乳化剂、表面活性剂(例如，乙氧基化脂肪醇、单硬脂酸甘油酯或磷酸酯)、稳定剂、抗氧化剂或防腐剂(例如，羟基苯甲酸酯)或其组合。例如，助溶剂和/或表面活性剂可用于将所述治疗剂以所需的浓度保持在溶液或悬浮液中。

[0062] 所述局部组合物可具有任何合适的剂型，如霜剂、洗剂、凝胶、软膏、摩丝、喷雾或气溶胶或任何经由穿透皮肤或粘膜吸收而施用药物的透皮装置(例如，贴剂)。在一些实施方案中，将所述局部组合物应用于皮肤或粘膜，覆盖约10-800cm^2、10-400cm^2或10-200cm^2的表面积。

III.包含渗透增强剂和另一种赋形剂的局部组合物

[0063] 在又另外的实施方案中，局部组合物包含司洛匹坦、渗透增强剂和至少一种亲脂性溶剂、制剂基质和增稠剂。在一些实施方案中，所述组合物包含亲脂性溶剂和制剂基质，或同一种物质既可用作亲脂性溶剂又可用作制剂基质。在另外的实施方案中，所述组合物包含亲脂性溶剂、制剂基质和增稠剂。所述组合物可任选地包含额外的治疗剂。在某些实施方案中，所述组合物包含无基质形式的司洛匹坦。

[0064] 所述渗透增强剂增加皮肤或粘膜对所述治疗剂的渗透性。渗透增强剂的非限制性实例包括：二甲基亚砜(DMSO)、癸基甲基亚砜、月桂氮卓酮、吡咯烷酮(例如，2-吡咯烷酮和N-甲基-2-吡咯烷)、表面活性剂、醇(例如，油醇)、聚乙二醇(例如，PEG 400)、二乙二醇单乙醚、油酸和脂肪酸酯(例如，肉豆蔻酸异丙酯、月桂酸甲酯、单油酸甘油酯和丙二醇单油酸酯)。

[0065] 亲脂性溶剂的非限制性实例包括：亲脂醇(例如，己二醇、辛基十二烷醇、油醇和硬脂醇)、聚乙二醇(例如，PEG 100、PEG 300、PEG 400和PEG 3350)、二乙二醇单乙醚、聚山梨醇酯(例如，Tween®20至80)、Labrasol®、脂肪酸酯(例如，肉豆蔻酸异丙酯和己二酸二异丙酯)、癸二酸二乙酯、单辛酸丙二酯、月桂酸丙二酯、单甘油酯和双甘油酯(例如，Capmul® MCM)、中链三酸甘油酯、辛酸/癸酸甘油三酯、单辛酸甘油酯、单油酸甘油酯、单亚油酸甘油酯、油酸甘油酯/丙二醇、矿物油和植物油。

[0066] 亲脂性溶剂还可用作制剂基质或载体。例如，聚乙二醇(例如，从PEG 100至PEG 3500，如PEG 300、PEG 400和PEG 3350)可用作亲脂性溶剂和制剂基质。

[0067] 所述组合物还可包含亲水性溶剂如C_1-C_5醇(例如，乙醇、异丙醇、甘油、丙二醇和1，2-戊二醇)和/或水。

[0068] 所述组合物可包含增稠剂以增加所述组合物的粘度和/或物理稳定性。增稠剂的实例包括但不限于：甘油、硬脂醇和聚合物(例如，聚二甲基硅氧烷[二甲基硅油]和Carbopol®聚合物)。

[0069] 在一些实施方案中，所述组合物还包含抗氧化剂。抗氧化剂的非限制性实例包括：丁基化羟基苯甲醚(BHA)、丁基化羟基甲苯(BHT)、生育酚(例如，维生素E及其酯)、类黄酮、谷胱甘肽、抗坏血酸及其酯、DMSO和螯合剂(例如，EDTA和柠檬酸)。

[0070] 在某些实施方案中，所述局部组合物包含按w/w计约0.5-10％或1-5％的司洛匹坦、约2-30％或5-20％的渗透增强剂、约20-80％或30-70％的还可用作制剂基质的亲脂性溶剂、约0.1-10％或1-7.5％的增稠剂和约0.01-2％或0.05-1％的抗氧化剂。作为非限制性实例，局部组合物可包含司洛匹坦、作为亲脂性溶剂和制剂基质的PEG 400和/或PEG 3350、作为渗透增强剂的二乙二醇单乙醚、油醇和/或肉豆蔻酸异丙酯、作为增稠剂的硬脂醇和作为抗氧化剂的BHT。

[0071] 所述局部组合物可具有任何合适的剂型，如霜剂、洗剂、凝胶、软膏、果冻、糊剂或任何通过经由皮肤或粘膜吸收而施用的透皮装置(例如，贴剂)。

IV.包含渗透增强剂和粘合剂的局部组合物

[0072] 在另外的实施方案中，局部组合物包含司洛匹坦、渗透增强剂和粘合剂。所述组合物可任选地包含额外的治疗剂。在某些实施方案中，所述组合物包含无基质形式的司洛匹坦。

[0073] 所述渗透增强剂增加皮肤或粘膜对所述治疗剂的渗透性。所述渗透增强剂可以是，例如，脂肪酸酯，其具有C_8-C_{20}或C_{12}-C_{18}的脂肪酰基链长和C_1-C_6或C_2-C_4醇组分(例如，异丙醇)。在某些实施方案中，所述渗透增强剂为肉豆蔻酸异丙酯或棕榈酸异丙酯。在一些实施方案中，所述渗透增强剂的量为按重量计所述组合物或透皮贴剂的皮肤接触层的约0.1-20％、0.5-15％、1-15％、2-12％或4-10％。

[0074] 所述粘合剂使所述局部组合物与皮肤或粘膜保持接触。粘合剂的非限制性实例包括：丙烯酸/丙烯酸酯(例如，聚丙烯酸酯，包括聚烷基丙烯酸酯和Duro-Tak®聚丙烯酸酯)、聚醋酸乙烯酯、乙烯乙酸乙烯酯共聚物、聚硅氧烷、聚氨酯、增塑聚醚嵌段酰胺共聚物、天然橡胶与合成橡胶、增塑丁苯橡胶嵌段共聚物(例如，Duro-Tak®87-6173)以及它们的混合物。

[0075] 所述局部组合物可包含一种或多种额外的赋形剂。所述额外的赋形剂可以是，例

如，稀释剂、润肤剂、增塑剂或减轻对皮肤或粘膜的刺激的试剂或其组合。

[0076] 在某些实施方案中，所述局部组合物在应用于皮肤或粘膜上之前基本上不含水、四甘醇(糖原质)和/或亲水性有机溶剂(例如，C_1-C_5醇)。

[0077] 所述组合物可透皮(包括穿透皮肤和经粘膜)施用所述治疗剂从而透过体表或膜(如完整无破损的皮肤或完整无破损的粘膜组织)进入全身循环。

[0078] 在一些实施方案中，所述局部组合物以透皮贴剂的形式施加在皮肤或粘膜上。所述贴剂具有层合或另外附接到支撑层的皮肤或粘膜接触层(简称“皮肤接触层”)。所述皮肤接触层在使用前可被可移动式释放衬里所覆盖以保护其皮肤接触表面并在将其施加到皮肤或粘膜之前保持其清洁。

[0079] 所述贴剂的支撑层起到支撑所述皮肤接触层的作用并用作屏障以防止所述皮肤接触层中的治疗剂散失到环境中。所述支撑层的材料与所述治疗剂、所述渗透增强剂和所述粘合剂相容，并且对所述贴剂的组分具有最低程度的可渗透性。所述支撑层可以是不透明的以保护所述贴剂的组分在暴露于紫外光中时不发生降解。所述支撑层还能够粘结并支撑粘结剂层，同时依然足够柔韧以适应使用所述贴剂的主体的运动。所述支撑层的材料可以是，例如，金属箔、金属化的多层箔、或含有聚合物(例如，聚酯[如聚酯对苯二甲酸酯]或铝化聚酯、聚乙烯、聚丙烯、聚四氟乙烯、聚乙烯甲基丙烯酸甲酯(polyethylene methyl methacrylate)嵌段共聚物、聚醚嵌段酰胺共聚物、聚氨酯、聚偏二氯乙烯、尼龙、硅酮弹性体、橡胶基的聚异丁烯、苯乙烯或苯乙烯-丁二烯或苯乙烯-异戊二烯共聚物)的复合箔或薄膜。所述释放衬里可由与所述支撑层相同的材料制成，或者可以是由适当的释放表面涂布的薄膜。

瘙痒

[0080] 瘙痒是一种在皮肤的感觉神经网络内的生理知觉，其与疼痛和物理或机械刺激一起，可以用作针对潜在身体威胁的预警系统。瘙痒是一种可以导致抓挠的难受感觉，但其与疼痛无关。国际瘙痒研究联合会(IFSI)将慢性瘙痒(相对于急性瘙痒)定义为持续六周或更长时间的瘙痒(S.Ständer等人，Acta Derm.Venereol.，2007，87(4)：291-4)。皮肤内和皮肤上的若干因素可以激活感觉神经纤维或调节其活性并因此触发、抑制或加剧瘙痒。物理刺激如冷和热调节瘙痒感；有痛感的热和冷可以使之显著减弱，而适度的冷使之加强(Valet等人，J.Invest.Dermatol.，2008，128(2)：426-33.)。机械因素如揉擦或抓挠皮肤可以通过激活神经纤维(其选择性地激活与失活大脑的某些区域)来短暂压制瘙痒(Yosipovitch等人，J.Invest.Dermatol.，2008，128(7)：1806-11)。

[0081] 慢性瘙痒因其难治和难忍，所以会严重降低其患者的生活质量。这是一种与慢性疼痛相当的、使人严重虚弱的病况，其可导致沮丧、绝望和抑郁。此外，长期的抓挠常常产生开放性皮肤病变、受到原发或继发感染、疤痕和潜在的毁容。慢性瘙痒常常是潜在疾病的指征，并且总是出现在诸如荨麻疹和特应性皮炎等疾病中。对潜在疾病的诊断是需要的，并且临床表现、病史和患者自评构成此类诊断的重要部分。

[0082] 根据Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften(AWMF)(德国科学医学会协会)的指导方针，伴随有慢性瘙痒症状的疾病和病症可依据皮肤是否发炎来分类(S.Ständer，Clin.Exp.Dermatol.，2006，31(6)：762-7)。IFSI还将瘙痒表征为皮肤性、全身性、神经源性、心因性、混合性等。非发炎性皮肤

上的慢性瘙痒可由皮肤病引起，包括特应性素质、皮肤干燥、卟啉病、日光损伤的类荨麻疹阶段、胆碱能性荨麻疹、肾上腺素能性荨麻疹、肥大细胞增多症的初始阶段、大疱性类天疱疮和杜林氏病(疱疹样皮炎)；可由内分泌和代谢性病症引起，如慢性肾功能不全及其治疗所需的透析、伴有胆汁淤积的肝病、糖尿病、营养吸收障碍、厌食、麸质肠病、甲状腺功能亢进、甲状腺功能减退、甲状旁腺功能亢进以及绝经期前后瘙痒；可由感染引起，包括HIV感染、寄生虫感染、幽门螺杆菌(Helicobacter pylori)感染以及蠕虫相关的感染；可由血液和淋巴增生性疾病引起，如铁缺乏症、真性红细胞增多症、嗜酸性粒细胞增多综合征、骨髓增生异常综合征、霍奇金病、非霍奇金淋巴瘤、浆细胞瘤、和系统性肥大细胞增多症；可由实体恶性肿瘤引起，包括宫颈癌、乳腺癌、前列腺癌或大肠癌以及类癌瘤；可由神经系统病症引起，如肱桡肌瘙痒、感觉异常性背痛、带状疱疹后遗神经痛、外阴疼痛、各种来源的神经病变、多发性硬化、肿瘤、脓肿、低灌注、涉及CNS/脊髓的梗塞；可由心因性障碍引起，如抑郁症、精神分裂症以及触幻觉；以及可由孕妇的肝内胆汁淤积症(妊娠瘙痒)引起。

[0083] 发炎性皮肤上的慢性瘙痒可在患有以下疾病的患者中观察到：炎症性皮肤病，包括但不限于特应性皮炎、过敏、刺激性接触性皮炎、干燥性皮炎、硬币状和出汗障碍性皮炎、扁平苔藓、硬化萎缩性苔藓、多形性日光疹牛皮癣，Grover病、粘蛋白增多症、肥大细胞增多症和荨麻疹；感染性皮肤病如霉菌病、细菌和病毒感染、疥疮、阴虱病、昆虫叮咬和毛囊炎；自身免疫性皮肤病，包括大疱性皮肤病、特别是疱疹样皮炎(杜林氏病)和大疱性类天疱疮；遗传性皮肤病如毛囊角化病(Darier's disease)、和家族性良性天疱疮(Hailey-Hailey disease)；妊娠相关的皮肤疾病，包括妊娠性多形疹(PEP，以前称为PUPPP)、妊娠期异位萌出和妊娠性类天疱疮；以及瘤形成如皮肤T细胞淋巴瘤(尤其是红皮病型)。

[0084] 结节性痒疹(prurigo nodularis)(PN，或写作结节性痒疹(nodular prurigo))是慢性瘙痒的一种特别严重的形式，其可采用本发明的方法和组合物治疗。由瘙痒、脱皮、苔藓丘疹和结节所表征，PN可发生于任何年龄段，但最常见于中老年患者的手臂和腿部(E.Weisshaar与S.Ständer,Acta Derm.Venereol.,2012,92:532-533)。PN的病因未知，但其常见于有特应性皮炎个人或家族史的患者，并且经常具有并发医学状况如肝或肾功能、皮肤局部创伤或损伤、感染以及HIV或其它免疫缺陷。PN可导致皮肤的永久性改变，包括结节性苔藓样硬化、角化过度、色素沉着过度和皮肤增厚。

采用司洛匹坦与其它止痒剂的组合疗法

[0085] 司洛匹坦可单独或与一种或多种另外的止痒剂组合用于治疗与任何病症相关的瘙痒(包括急性和慢性瘙痒)。瘙痒的感觉可源于，例如，周围神经系统(例如，皮肤或神经性瘙痒)或中枢神经系统(例如，神经性、神经源性或心因性瘙痒)。

[0086] 瘙痒相关的病况的实例包括但不限于本文别处及以下所述的那些：皮肤疾症和病况(包括发炎和非发炎的皮肤状况)，包括但不限于：成人blaschkitis、淀粉样变性(例如，原发性皮肤淀粉样变性[包括斑疹性淀粉样变性、苔藓样淀粉样变性和结节性淀粉样变性])、烧伤(例如，化学烧伤、晒伤)、皮炎{例如，特应性皮炎、接触性皮炎(包括过敏性接触性皮炎、刺激性接触性皮炎和光皮炎)、湿疹(例如，自体敏感性皮炎、疱疹样皮炎[杜林氏病]、盘状湿疹、出汗障碍[汗疱疹]、手部湿疹、ID反应[泛发性湿疹]、钱币状湿疹、停滞性皮炎[引力性湿疹]、静脉性湿疹和干燥性湿疹)、脓疱性皮炎(例如，嗜酸性脓疱性毛囊炎[Ofuji病]、反应性关节炎[莱特尔氏病]和角层下脓疱性皮肤病[威尔金森病])、以及脂溢

性皮炎(例如,婴儿脂溢性皮炎、莱内氏病和单纯糠疹脱发[头皮屑])}、红皮病(剥脱性皮炎)、毛囊炎、须部假性毛囊炎(理发痒)、化脓性汗腺炎、鱼鳞病(例如,寻常性鱼鳞病、先天性鳞癣、表皮松解性角化过度和片层状鱼鳞癣)、扁平苔藓(例如,皮肤扁平苔藓与口腔扁平苔藓)、硬化性苔藓(例如,外阴硬化性萎缩性硬化性苔藓等)、单纯苔藓(例如,慢性单纯性苔癣[神经性皮炎])、线状IgA大疱性皮肤病(线状IgA皮肤病)、红斑狼疮(例如,皮肤红斑狼疮、盘状红斑狼疮和系统性红斑狼疮)、痱子(汗疹)、掌跖角化症(例如,点状掌跖角化病)、糠疹(例如,石棉状糠疹、苔藓样糠疹[包括慢性苔藓样糠疹和急性痘疮样苔藓样糠疹]、玫瑰糠疹、毛发红糠疹[德弗札病]和花斑癣)、痒疹(例如,光化性痒疹、贝尼埃痒疹、结节性痒疹、色素性痒疹和单纯痒疹)、肛门瘙痒、阴囊瘙痒、外阴瘙痒、牛皮癣(例如,红皮病型银屑病、滴状牛皮癣[发疹性银屑病]、寻常性银屑病[慢性固定性银屑病]、脓疱性银屑病和掌跖脓疱病)、副银屑病(例如,大斑块型副银屑病和小斑块型副银屑病[慢性浅表性皮炎])、痒点(痒点)、皮疹(例如,擦烂和口周皮炎)、酒渣鼻、荨麻疹(例如,接触性荨麻疹[包括荨麻疹]和特发性荨麻疹)、白癜风、皮肤干燥(干性皮肤)、皮肤皲裂(例如,脚干裂)、头皮瘙痒、结痂愈合、瘢痕发育和痣的发生、粉刺和向内生毛;

医疗病症和病况(包括外周和全身性疾病),包括但不限于:特应性素质、自身免疫性疾病(例如,乳糜泻、皮肌炎、Graves病、类天疱疮[例如,大疱性类天疱疮]、硬皮病和Sj□gren综合征)、血液病(例如,贫血[例如,缺铁性贫血和镰状细胞性贫血]、高钙血症、骨髓增生异常综合征和红细胞增多症[例如,真性红细胞增多症])、克雅氏病(例如,肮瘙痒)、糖尿病、遗传性疾病(例如,Alagille综合征、Darier病、大疱性表皮松解症、家族性良性天疱疮和sj□gren-拉尔森综合征)、Grover病、HIV/AIDS、肾脏疾病(例如,糖尿病肾病、肾小球肾炎、慢性肾脏病、终末期肾脏疾病和慢性肾衰竭)、尿毒症(例如尿毒症皮肤瘙痒[肾瘙痒])、肝脏疾病(例如,肝硬化[例如,原发性胆汁性肝硬化]、肝炎[包括甲型肝炎、乙型肝炎、丙型肝炎、丁型肝炎、戊型肝炎及其慢性病症]以及肝衰竭)、胆汁淤积(例如,胆汁淤积性瘙痒)、黄疸(例如,胆汁性瘙痒)、淋巴结病(例如,淋巴结肿大)、肥大细胞疾病(例如,肥大细胞活化综合征和肥大细胞增多症)、多发性硬化症、神经病变(例如,外周神经病变[例如,肱桡肌瘙痒、感觉异常性背痛、神经病、小纤维周围神经病变])、神经刺激、挤压神经、甲状旁腺疾病(例如,甲状旁腺功能亢进、甲状旁腺功能减退症)、甲状腺疾病(例如,甲亢、甲状腺功能减退、粘液性水肿)、中风、癌症{例如,类癌综合征、白血病(例如,皮肤白血病和淋巴白血病)、淋巴瘤(例如,霍奇金病和非霍奇金淋巴瘤[例如,皮肤B细胞淋巴瘤和皮肤T细胞淋巴瘤(包括蕈样肉芽肿和Sézary病)])、卡波氏肉瘤、多发性骨髓瘤和皮肤癌}、肿瘤(例如,脑肿瘤、浆细胞瘤及宫颈、结肠和前列腺的实体肿瘤)、副肿瘤性皮肤瘙痒、精神疾病(例如,压力、焦虑症、寄生虫妄想症、抑郁症、强迫症[例如,神经官能症性表皮剥脱]以及触觉的幻觉)、老化(例如,老年皮肤瘙痒)、与衰老相关的激素平衡的改变(例如,停经期前症候和绝经);

感染和侵染,包括但不限于:尾蚴性皮炎(游泳者的痒)、昆虫叮咬(例如,由蚂蚁、蜜蜂、恙螨、跳蚤、虱子[包括体虱、头虱和阴虱]、螨虫、蚊子、蜘蛛、蜱和黄蜂)、疥疮、细菌性感染(例如,脓肿、坏疽性皮炎、脓疱、红癣,脓疱病和莱姆病)、真菌感染(如念珠菌病、脚气、体癣[体癣]、股癣[股癣]和脚癣[脚癣])、病毒感染(如疱疹{包括带状疱疹[带状疱疹]和带状疱疹痒)、麻疹、细小病毒感染(例如,细小病毒B19)、水痘(水痘)和黄热病}、和蠕虫感染{如蠕虫(例如,蠕虫病[蠕虫病])、钩虫(例如,皮肤幼虫移行症)、盘尾属蠕虫(如盘尾丝虫病[河

盲])、蛲虫、蛔虫(如丝虫病和旋毛虫病)和血吸虫属蠕虫(例如,血吸虫病)};

对过敏原和刺激物的反应,包括但不限于:过敏性鼻炎(如花粉症[包括枯草热])、哮喘、动物过敏原(如猫的皮屑,狗毛)、化学过敏原(如酸[例如,枞酸和山梨酸]、化妆品、清洁剂、染料、织物柔软剂、杀菌剂、羟乙基淀粉、胶乳)、食物过敏原(例如,牛奶蛋白、花生、坚果、海鲜、香料、防腐剂[例如,硝酸盐]、维生素[例如,维生素A和B]、酒精、咖啡因和谷氨酸钠)、金属和金属盐的过敏原(如铬、钴、金和镍及其盐)、植物过敏原(如秘鲁香脂和漆酚[例如,毒常春藤、毒橡树和漆树])、化学刺激物(如酸、碱、金属加工液、溶剂、表面活性剂、洗涤剂、肥皂、清洁用品、化妆品、香水、除臭剂、止汗剂、食用香精、香料、防腐剂[例如,甲醛和对羟基苯甲酸酯类]、单体和聚合物[例如,丙烯酸树脂、环氧树脂、环氧乙烷、乳胶和漆]、油[例如,煤油])、织物(如羊毛)、植物刺激物(如烷基间苯二酚[例如,红花银桦(Grevillea banksii)、银桦(Grevillea"Robyn Gordon")和银杏(Gingko biloba)])以及物理刺激物(如水[例如,aquadynia和水源性瘙痒)、来自空调的低湿度、和低温);

药物/药物疗法引起的瘙痒,包括但不限于:氯喹、羟乙基纤维素、羟乙基淀粉、血管紧张素转换酶抑制剂、黄嘌呤氧化酶抑制剂(如别嘌呤醇)、抗生素(如异烟肼、新霉素、青霉素、磺胺类药物和万古霉素),抗真菌药物(如氟康唑、灰黄霉素、伊曲康唑和酮康唑)、神经镇静药/抗精神病药物(如酚噻嗪类),抗心律失常药物(如胺碘酮与奎尼丁)、化疗药、利尿药(如氢氯噻嗪)、他汀类药物(如辛伐他汀)、和激活组胺H_1受体或引起组胺释放的药物(如阿片);以及

妊娠相关的病况,包括但不限于:妊娠性类天疱疮、疱疹样脓疱病、妊娠期肝内胆汁淤积症(妊娠瘙痒)、妊娠多形疹、妊娠痒疹、妊娠瘙痒性毛囊炎和妊娠瘙痒性荨麻疹样丘疹及斑块。

[0087] 一种或多种另外的止痒剂可任选地与司洛匹坦组合用于治疗瘙痒(包括急性和慢性瘙痒)。止痒剂的实例包括但不限于:

抗组胺剂,包括但不限于:抑制组胺H_1受体活动的抗组胺剂(例如,阿伐斯汀、安他唑啉、氮卓斯汀、比拉斯汀,溴苯那敏、布克利嗪、溴苯海拉明、卡比沙明、西替利嗪,氯丙嗪,赛克利嗪、扑尔敏、氯苯海拉明、斯汀、赛庚啶、地氯雷他定、右溴苯那敏、右氯苯那敏、茶苯海明、二甲茚定、苯海拉明、多虑平、多西拉敏、依巴斯汀、恩布拉敏、非索非那定、羟嗪、左西替利嗪、氯雷他定、美克洛嗪、吡拉明、米氮平、奥洛他定、奥芬那君、苯茚胺、非尼拉敏、苯托沙敏、异丙嗪、美吡拉敏、喹硫平、卢帕他定、曲比那敏和曲普利啶)以及抑制组胺H_4受体活动的抗组胺剂(如噻普酰胺、JNJ 7777120和VUF-6002)以及它们的类似物和衍生物;

血清素受体拮抗剂,包括但不限于:5-HT_2受体拮抗剂(如氯氮平、赛庚啶、酮色林、苯噻啶、喹硫平)和5-HT_3受体拮抗剂(例如,阿洛司琼、西兰司琼、多拉司琼、格拉司琼、昂丹司琼、帕洛诺司琼和托烷司琼)以及它们的类似物和衍生物;

神经激肽-1(NK-1)受体拮抗剂,包括但不限于:阿瑞吡坦、卡索吡坦(GW679769)、达匹坦、依洛匹坦、福沙吡坦、拉奈匹坦(LY-303870)、maropitant、netupitant、nolpitant、奥维匹坦、罗拉吡坦、维替匹坦、沃氟匹坦、AV-818、BIIF 1149CL、CP122,721、DNK-333、GSK-424887、L-733060、L-759274、LY-686017、M516102和TA-5538以及它们的类似物和衍生物;

阿片受体拮抗剂,包括但不限于:布托啡诺、cyprodime、利瓦洛凡(酒石酸烯丙左吗喃或丙烯羟吗啡烷)、纳布啡、烯丙吗啡(烯丙吗啡或纳洛芬)、纳洛酮、naloxol、纳美芬、纳曲

酮(如纳曲酮1％霜剂)和纳曲醇以及它们的类似物和衍生物；

阿片受体激动剂，包括但不限于：选择性κ阿片受体激动剂(如阿西马多林、布马佐辛、强啡肽、依那朵林、酮唑辛、纳呋拉啡、salvinorin A、2-甲氧甲基salvinorin B、2-乙氧甲基salvinorin B、2-氟乙氧甲基salvinorin B、舒芬太尼、替氟朵、BRL-52537、FE 200665、GR-89696、HZ-2、ICI-199，441、ICI-204，448、LPK-26、U-50488和U-69，593)以及它们的类似物和衍生物；

Janus激酶(JAK)抑制剂，包括但不限于：JAK1抑制剂(例如，GLPG0634和GSK2586184)、JAK2抑制剂(例如，lestaurtinib、pacritinib、CYT387和TG101348)、JAK1/JAK2抑制剂(例如，baricitinib和卢索替尼)和JAK3抑制剂(例如，托法替尼)以及它们的类似物和衍生物；

免疫调节剂和免疫抑制剂，包括但不限于沙利度胺、抗代谢药(例如，抗叶酸剂如氨甲喋呤)和钙调磷酸酶抑制剂(如环孢菌素[环孢菌素]、吡美莫司和他克莫司)以及它们的类似物和衍生物；

抗抑郁药，包括但不限于：三环类抗抑郁药(例如，阿米替林、氧阿米替林、阿莫沙平、二苯噻庚英[度硫平]、多虑平和美利曲辛)、四环类抗抑郁药(例如，阿莫沙平，麦普替林、马吲哚、米安色林、米氮平和司普替林)、选择性血清素再摄取抑制剂(SSRI，例如，西酞普兰、达泊西汀、西酞普兰、氟西汀、氟伏沙明、帕罗西汀和舍曲林)和5-羟色胺去甲肾上腺素再摄取抑制剂(SNRI，例如，比西发定、度洛西汀、米那普仑、左旋米那普仑、西布曲明、文拉法辛、去甲文拉法辛和SEP-227162)以及它们的类似物和衍生物；

抗惊厥药，包括但不限于：卡马西平、加巴喷丁、普瑞巴林和丙戊酸及其盐类(例如，丙戊酸钠)以及它们的类似物和衍生物；

皮质类固醇，包括但不限于：氢化可的松类(例如，可的松及其衍生物[例如，醋酸可的松]、氢化可的松及其衍生物[例如，醋酸氢化可的松、17-醋丙酸氢化可的松、17-丁丙酸氢化可的松、17-丁酸氢化可的松和17-戊酸氢化可的松]、泼尼松龙、甲泼尼龙及其衍生物[例如，醋丙酸甲泼尼龙]、强的松和替可的松及其衍生物[例如，替可的松匹伐酯])、倍他米松类(例如，倍他米松及其衍生物[例如，二丙酸倍他米松、倍他米松磷酸钠和戊酸倍他米松]、地塞米及其松衍生物[例如，地塞米松磷酸钠]和氟考龙及其衍生物[例如，己酸氟考龙和特戊酸氟考龙])、卤代类固醇(例如，阿氯米松及其衍生物[例如，二丙酸阿氯米松]、倍氯米松及其衍生物[例如，二丙酸倍氯米松]、氯倍他索及其衍生物[例如，17-丙酸氯倍他索]、氯倍他松及其衍生物[例如，17-丁酸氯倍他松]、去羟米松及其衍生物[例如，醋酸去羟米松]、二氟拉松及其衍生物[例如，二醋酸二氟拉松]、二氟可龙及其衍生物[例如，戊酸二氟可龙]、氟泼尼定及其衍生物[例如，醋酸氟泼尼定]、氟替卡松及其衍生物[例如，丙酸氟替卡松]、卤倍他索[乌倍他索]及其衍生物[例如，丙酸卤倍他索]、卤米松及其衍生物[例如，醋酸卤米松]和莫米松及其衍生物[例如，糠酸莫米松])、丙酮化合物及有关物质(例如，安西缩松、布地奈德、环索奈德、地奈德、醋酸氟轻松、肤轻松(fluocinolone acetonide)、氟氢缩松(flurandrenolide[flurandrenolone或fludroxycortide])、哈西奈德、曲安奈德和曲安西龙醇(triamcinolone alcohol))和碳酸酯(例如，泼尼卡酯)以及它们的类似物和衍生物；

局部麻醉剂，包括但不限于：酰胺类(如阿替卡因、布比卡因、可卡因[地布卡因]、依替卡因、布比卡因、利多卡因[例如，利多卡因2.5-5％霜剂]、丙胺卡因[例如，丙胺卡因2.5％霜剂]、EMLA[利多卡因2.5％/丙胺卡因2.5％霜剂]、甲哌卡因、罗哌卡因和美索卡因)、酯类

(如苯佐卡因、氯普鲁卡因、可卡因、环甲卡因、二甲卡因[拉罗卡因]、哌哌卡因、普鲁卡因[奴佛卡因]、丙美卡因,丙氧卡因、斯妥伐因和四卡因[丁卡因])、醚类(例如,聚多卡醇[例如,聚多卡醇3%泡沫]和普莫卡因[丙吗卡因][例如,丙吗卡因1%霜剂])和自然衍生的局部麻醉剂(例如,可卡因、丁香酚、薄荷醇、石房蛤毒素、新石房蛤毒素和河豚毒素)以及它们的类似物和衍生物;

抗刺激药和冷却剂,包括但不限于:辣椒素、樟脑、薄荷油、薄荷醇(如薄荷醇1-3%霜剂)、和苯酚(例如,在炉甘石洗剂中)以及它们的类似物和衍生物;

湿润剂,包括但不限于:水性保湿剂、含酸(例如,乳酸)的低pH值保湿剂和含有吸引和保留水分的湿润剂(如甘油、山梨醇、乳酸、尿素、透明质酸和其盐)的保湿剂、防止蒸发的密闭剂{如油(如矿物油、有机硅油[例如,二甲基硅油])和石油凝胶(矿脂)}和/或提供部分水化和吸收的软化剂(如油、蜡[例如,羊毛脂和石蜡]、脂质[例如,磷脂、神经酰胺、甘油三酯、乙二醇硬脂酸酯、硬脂酸甘油酯、脂肪酸和角鲨烯]和甾醇[例如,胆固醇和植物甾醇])以及它们的类似物和衍生物;以及

其它种类的止痒剂,包括但不限于:S-腺苷甲硫氨酸、肉毒毒素(如肉毒杆菌毒素A型和B型)、维生素D及其类似物和衍生物(例如,骨化三醇和卡泊三醇[卡泊三醇(calcipotriene)])、非甾体类抗炎药(NSAID,如阿司匹林)、大麻素受体激动剂(例如,CB_2激动剂,如十六酰胺乙醇)、细胞因子抑制剂(例如,针对白细胞介素如IL-31的抗体)、前列腺素D_2受体的(DP_1)拮抗剂和/或在Th_2细胞上表达的化学引诱物受体的同源分子(CRTH2)(例如,TS-022)、磷酸二酯酶(PDE)抑制剂(例如,PDE4抑制剂,如阿普斯特)、蛋白酶激活受体2(PAR2)拮抗剂(例如,GB83)、瞬时受体电位辣椒素(vanilloid)(TRPV)拮抗剂(例如,TRPV1拮抗剂,如辣椒平和SB-705498)、神经营养酪氨酸激酶受体抑制剂(例如,TrkA抑制剂,如CT327)、抗微生物剂(包括抗生素、抗真菌剂、抗病毒剂、抗寄生物剂,如克罗米酚和利福平[利福平])、胆汁吸收减少或胆汁螯合剂(如熊去氧胆酸[熊去氧胆酸])、紫外辐射(如紫外线A和B)和治疗瘙痒相关病况的的潜在原因的治疗剂以及它们的类似物和衍生物。

[0088] 如果需要(例如,用于在白天缓解瘙痒),可使用无镇静作用的止痒剂。例如,第二代和第三代抗组胺剂被设计为无镇静作用或相比第一代抗组胺剂镇静作用较弱。第二代和第三代抗组胺剂的非限制性实例包括:阿伐斯汀、阿司咪唑、氮卓斯汀、贝他斯汀、比拉斯汀、西替利嗪、左西替利嗪、依巴斯汀、非索非那定、酮替芬、左卡巴斯汀、氯雷他定、地氯雷他定、咪唑斯汀、奥洛他定、奎非那定、卢帕他定和特非那定。

[0089] 在一些实施方案中,将具有适中或中等功效的皮质类固醇与司洛匹坦组合用于治疗瘙痒相关的病况。具有适中或中等功效的皮质类固醇的实例包括:7-组美国分类体系下的III、IV和V组皮质类固醇以及4-类欧洲分类体系下的II类皮质类固醇,包括但不限于:安西缩松0.1%(例如,霜剂)、二丙酸倍他米松0.05%(例如,Diprosone®霜剂/软膏)、戊酸倍他米松0.1%(例如,霜剂/软膏)、丁酸氯倍他松0.05%(例如,Eumovate®霜剂)、地奈德0.05%(例如,Tridesilon®霜剂/软膏和DesOwen®霜剂/软膏)、氟轻松0.01-0.2%(例如,Synalar®霜剂/软膏和Synemol®霜剂)、氟氢缩松0.05%(例如,Cordran®条带)、丙酸氟替卡松0.005%(例如,Cutivate®软膏)、丙酸氟替卡松0.05%(例如,Cutivate®霜剂)、卤米松0.05%(例如,霜剂)、丁酸氢化可的松0.1%(例如,Locoid®霜剂/软膏)、戊酸氢化可的松0.2%(例如,Westcort®霜剂/软膏)、糠酸莫米松0.1%(例如,Elocon®霜剂/

软膏)、曲安奈德0.025-0.5%(例如,Aristocort®霜剂/软膏、Kenacomb®霜剂/软膏、Kenalog®霜剂和Viaderm®KC霜剂/软膏)和双乙酸呋曲安奈德0.5%(例如,霜剂/软膏);

[0090] 可向患有瘙痒的主体施用与司洛匹坦同时施用(例如,在含司洛匹坦的同一组合物中,或在单独的组合物中)或序贯施用(之前或之后)的任选的另外的止痒剂。司洛匹坦和所述任选的另外的止痒剂可以在任何合适模式中独立施用,包括但不限于:口服、局部(例如,皮肤/外表皮、经皮、经粘膜、透粘膜、鼻内[例如,通过鼻腔喷雾或滴剂]、经眼(opthalmically)[例如,通过滴眼液]、经肺[例如,经吸入]、颊面、舌下、直肠和阴道),通过注射或输注(例如,胃肠外,包括肌内、皮下、皮内、静脉内/血管内以及鞘内)以及通过植入(例如,皮下和肌内)。在一些实施方案中,如果瘙痒是局部性的,则局部(例如,皮肤)施用止痒剂,而如果瘙痒分布广泛(普遍的)或有全身性成因,则全身施用(例如,口服或静脉内)止痒剂。在某些实施方案中,口服施用司洛匹坦和/或所述任选的另外的止痒剂。在其它实施方案中,局部施用(例如,皮肤、粘膜、颊面或舌下)司洛匹坦和/或所述任选的另外的止痒剂。

[0091] 司洛匹坦和所述任选的另外的止痒剂可以任何合适的频率独立施用,包括但不限于:每天(一次、两次、三次或更多次/天)、每两天、每周两次、每周三次、每周、每两周、每三周、每个月、每两个月以及每三个月。给药频率可取决于,例如,所选用的给药模式。例如,司洛匹坦的皮肤制剂和/或所述任选的另外的止痒剂的皮肤制剂可以一天两次、三次或四次,应用于主体的皮肤。在一些实施方案中,遵循长期给药方案施用司洛匹坦(serlopitant)。在某些实施方案中,在至少2周、3周、1个月、1.5个月、2个月、3个月、4个月、5个月、6个月或更长的时间段上施用司洛匹坦。

[0092] 局部剂型的实例包括但不限于:霜剂、软膏、凝胶、擦剂、洗剂、栓剂(例如,直肠和阴道栓剂)、颊面和舌下片剂与丸剂、喷雾(例如,皮肤和鼻腔喷雾)以及滴剂(例如,滴眼液、滴鼻液和滴耳液)。口服剂型的非限制性实例包括:固体剂型(例如,扁囊剂、胶囊和片剂)和液体剂型(例如,水性液体和/或非水性液体中的溶液或悬浮液,以及水包油液体乳状液或油包水液体乳状液)。在注射用制剂的非限制性实例中,所述制剂为溶液的形式并且包含止痒剂(例如,局部麻醉剂)、媒介物(例如,水基媒介物或无菌水)、缓冲剂、还原剂/抗氧化剂(例如,焦亚硫酸钠,如果使用肾上腺素作为血管收缩剂)和防腐剂(例如,对羟基苯甲酸甲酯)以及任选血管收缩剂(例如,肾上腺素)以通过收缩血管,从而在延长的持续时间内浓缩所述止痒剂并增加所述止痒剂的最大剂量,以此来增加所述止痒剂药效的持续时间。

[0093] 表4提供了采用司洛匹坦和一种或多种另外的止痒剂的组合疗法的非限制性实例,所述组合疗法用于治疗与各种病症相关的瘙痒。表4还示出了用于治疗所述病况的潜在成因的其它治疗剂。

表4:

除司洛匹坦以外的药剂	病况
皮质类固醇	皮肤发炎、皮肤皲裂、过敏性皮炎、接触性皮炎、湿疹、脂溢性皮炎、红皮病、扁平苔藓，慢性单纯性苔藓、地衣硬化、红斑狼疮、银屑病、皮疹、疥疮和烧伤（如晒伤）
抗组胺剂（例如，局部用多虑平以及镇静苯海拉明或非镇静口服西替利嗪））	荨麻疹、过敏性皮肤瘙痒、局部皮肤瘙痒（如昆虫叮咬）和全身皮肤瘙痒（如水痘）
局部麻醉剂 + 任选的抗刺激药/冷却剂	局部瘙痒（例如，昆虫叮咬）及轻度至中度瘙痒
抗刺激药（例如，辣椒碱）	慢性局部瘙痒（例如，感觉异常性背痛和结节性痒疹）
湿润剂和/或炉甘石	过敏性皮疹（例如，毒藤/毒橡树和荨麻疹）、烧灼（例如，晒伤）和昆虫叮咬
湿润剂 + 任选的抗刺激药/冷却剂	特应性皮炎、接触性皮炎、湿疹、皮脂溢性皮炎、鱼鳞病、牛皮癣和干燥症

免疫调节剂（例如，他克莫司）+ 任选的皮质类固醇	特应性皮炎
JAK抑制剂（例如，托法替尼）或PDE抑制剂（例如，阿普斯特）或维生素D（例如，钙泊三醇）	牛皮癣
TrkA抑制剂（例如，CT327）	特应性皮炎、牛皮癣和皮肤T细胞淋巴瘤
JAK抑制剂（例如，卢索替尼）	贫血、周围神经病变和真性红细胞增多症
阿司匹林（局部用）	慢性单纯性苔藓
三环类抗抑郁药（例如，多虑平）	慢性重度瘙痒
阿片受体拮抗剂（例如，纳络酮）	肾病与胆汁淤积性疾病的顽固性瘙痒
1) 紫外线B光线疗法 + 促红细胞生成素；或 2) 消胆胺 + 阿片受体拮抗剂（例如，纳曲酮）+ 活性炭；或 3) 沙利度胺（Thalidomide）	慢性肾病
1) 离子交换树脂（例如，消胆胺）+ 阿片受体拮抗剂（例如，纳络酮）；或 2) SSRI、S-腺苷甲硫氨酸、利福平和/或熊去氧胆酸；或 3) 消胆胺 + 阿片受体拮抗剂（例如，纳美芬）+ 血清素拮抗剂（例如，昂丹司琼）+ 熊去氧胆酸 + 利福平 + 任选的亮光疗法；或 4) 紫外线B + 大麻素（例如，屈大麻酚）	胆汁淤积
1) 抗刺激药（例如，辣椒碱）+ 紫外线B光线疗法 + 任选的活性炭 + 任选的低pH湿润剂；或	尿毒症（尿毒性瘙痒）

2)κ阿片受体激动剂（例如，纳呋拉啡）+ 任选的紫外线B	
紫外线B光线疗法	水源性皮炎、特应性皮炎、HIV/AIDS以及结节性痒疹
紫外线A光线疗法 + 补骨脂素	湿疹、牛皮癣、白癜风以及皮肤T细胞淋巴瘤
1)紫外线A光线疗法 + 补骨脂素；或 2)SSRI（例如，帕罗西汀）、阿司匹林和/或α干扰素	真性红细胞增多症
血清素受体拮抗剂（例如，昂丹司琼）（与阿片样物质同时）+ 阿片受体拮抗剂（例如，纳布啡）（与阿片样物质同时）	脊髓性阿片样物质诱导的瘙痒
安定药（例如，哌迷清）+ SSRI（例如，氟伏沙明）	瘙痒性精神障碍（例如，神经官能症性表皮剥脱）

司洛匹坦作为安眠药的用途

[0094] 本发明还涵盖司洛匹坦作为安眠药(sleep aid)的用途。因此，本发明提供帮助睡眠的方法，包括向患有睡眠问题或障碍的主体施用有效量的司洛匹坦或其药学上可接受的盐、溶剂合物或多晶型物。任选地，还可向主体施用另外的睡眠辅助药剂。

[0095] 司洛匹坦可帮助患有睡眠障碍或一般性睡眠问题的主体睡眠。作为安眠药，司洛匹坦可具有镇静效果(缓解烦躁、焦虑或兴奋)和/或催眠效果(引起、维持和/或延长睡眠)。

[0096] 可能由司洛匹坦缓解的睡眠障碍的实例包括但不限于：失眠(包括原发性和继发性失眠以及短暂的、急性和慢性失眠)、昏睡病(非洲锥虫病)、昼夜节律睡眠障碍(例如，晚期睡眠相位紊乱[ASPD]、睡眠相位后移综合征[DSPD]、不规律的睡眠觉醒节律、非24小时睡眠觉醒障碍、时差和轮班工作睡眠障碍[SWSD])、异态睡眠(例如，磨牙症、快速眼动睡眠行为障碍[RBD]、周期性肢体运动障碍[PLMD或夜间肌阵挛]、不宁腿综合征[RLS]、睡眠麻痹、爆炸头综合症、夜惊[夜惊(night terror)或夜惊(Pavor nocturnus)]、夜尿、夜间进食综合征、梦话[梦呓]、梦游[梦行症]和睡眠恐惧症)；以及呼吸相关的睡眠障碍(如睡眠呼吸暂停[包括中央、阻塞性和混合性睡眠呼吸暂停]、低通气综合征、睡眠相关的通气不足、打鼾和上气道阻力综合征)。

[0097] 在主体想睡觉时(例如，夜间或临睡时)施用司洛匹坦用作安眠药。施用有效量的司洛匹坦以帮助睡眠。所述有效量可取决于各种因素，包括：施用模式；主体的年龄、体重、身体状况、性别和膳食；睡眠问题的严重程度；以及主体对治疗的反应。在某些实施方案中，作为安眠药的司洛匹坦的剂量为约0.1-500mg或约0.25-400mg或约0.5-300mg或约1-200mg或约2.5-100mg或约5-50mg，或主治医生认为适当的量。可施用单个剂量或多个剂量的司洛匹坦以帮助睡眠。在另外的实施方案中，用于帮助睡眠的司洛匹坦的剂量为约0.01-10mg/kg、0.025-7.5mg/kg、0.05-5mg/kg、0.075-2.5mg/kg或0.1-1mg/kg体重，或主治医生认为适当的量。

[0098] 司洛匹坦可经任何合适的途径施用。司洛匹坦可能的施用途径包括但不限于：口

服、肠外(包括肌内、皮下、皮内、静脉内、动脉内、髓内和鞘内)、腹膜内和局部(包括皮肤/外表皮、经皮、粘膜、经粘膜、鼻内[例如,通过鼻腔喷雾或滴鼻液]、眼内[例如,通过滴眼液]、肺内[例如,经吸入]、颊面、舌下、直肠和阴道)。在某些实施方案中,口服施用司洛匹坦。

[0099] 在其它实施方案中,司洛匹坦通过颊面或舌下片剂或丸剂局部施用。所述颊面或舌下片剂或丸剂可被设计成以提供司洛匹坦的更快释放从而更迅速地将其纳入全身循环。除治疗有效量的司洛匹坦以外,所述颊侧或舌下片剂或丸剂可以包含合适的赋形剂,包括但不限于填充剂与稀释剂的任何组合(例如,甘露醇和山梨醇)、结合剂(例如,碳酸钠)、润湿剂(例如,碳酸钠)、崩解剂(例如,交联聚维酮和交联羧甲基纤维素钠)、润滑剂(例如,二氧化硅[包括二氧化硅胶体]和硬脂酰富马酸钠)、稳定剂(例如,碳酸氢钠)、矫味剂(例如,薄荷味)、甜味剂(例如,三氯蔗糖)以及染色剂(例如,氧化铁黄)。可受益于安眠药的颊面或舌下片剂或丸剂的患者群体的非限制性实例是那些过早醒来并难以再次入睡的患者。

[0100] 在一些实施方案中,将(一种或多种)另外的睡眠辅助药剂与司洛匹坦组合施用以帮助睡眠。所述另外的睡眠辅助药剂可以与施用司洛匹坦同时施用或序贯施用(之前或之后)。如果与司洛匹坦同时施用,所述另外的睡眠辅助药剂可被包含在含司洛匹坦的同一组合物中,或是单独的组合物中。使用司洛匹坦可减少另外的睡眠辅助药剂原本所需的剂量和/或治疗长度,并从而最小化或避免所述另外的睡眠辅助药剂的任何不良反应(例如,依赖性或成瘾性)。

[0101] 所述另外的睡眠辅助药剂可视其催眠性能或其治疗睡眠障碍或睡眠障碍的潜在成因的能力(例如,压力、焦虑、抑郁或神经状况)来选择。在一些实施方案中,所述另外的睡眠辅助药剂选自:催眠药、镇静剂、抗焦虑药、安定药以及抗抑郁药。具体的睡眠辅助药剂可具有落入多个类别(例如,苯二氮䓬类药物在较低剂量时可具有镇静或抗焦虑效果,而在较高剂量时可具有催眠效果)的药效。在另外的实施方案中,所述另外的睡眠辅助药剂选自:

抗抑郁药,包括三环类抗抑郁药(例如,阿米替林、氧阿米替林、阿莫沙平、氯丙咪嗪、地昔帕明、二苯噻庚英[度硫平]、多虑平、丙咪嗪、洛非帕明、美利曲辛、去甲替林、普罗替林、三甲丙咪嗪)、四环类抗抑郁药(例如,阿莫沙平、麦普替林、马吲哚、米安色林、米氮平和司普替林)、选择性血清素再摄取抑制剂(SSRI,例如,西酞普兰、达泊西汀、西酞普兰、氟西汀、氟伏沙明、帕罗西汀和舍曲林)、5-羟色胺拮抗剂和再摄取抑制剂(SARI,如依托哌酮、洛吡哌唑、lubazodone、美吡哌唑、奈法唑酮、曲唑酮)、5-羟色胺去甲肾上腺素再摄取抑制剂(SNRI,如比西发定、度洛西汀、米那普仑、左旋米那普仑、西布曲明、文拉法辛、去甲文拉法辛和SEP-227162)和单胺氧化酶(MAO)抑制剂(包括选择性MAO-A抑制剂,如吗氯贝胺、吡吲哚[吡吲哚]和托洛沙酮[托洛沙酮])及其类似物和衍生物;)

抗精神病药,包括第一代(或典型的)抗精神病药(包括吩噻嗪[例如,氯丙嗪、氟奋乃静、左美丙嗪、培拉嗪、氰噻嗪、奋乃静、哌泊噻嗪、丙氯拉嗪、丙嗪、异丙嗪、硫丙拉嗪、硫利达嗪和三氟拉嗪]和噻吨[例如,氯哌噻吨、珠氯噻醇、氟哌噻吨和氨砜噻吨])和第二代(或非典型)抗精神病药(例如,氨磺必利、阿立哌唑、阿塞那平、氯氮平、伊潘立酮、洛沙平、阿莫沙平、鲁拉西酮、奥氮平、喹硫平、norquetiapine、利培酮、帕潘立酮、舍吲哚、曲米帕明、齐拉西酮和佐替平)以及它们的类似物和衍生物;

抑制组胺H_1受体活动的抗组胺剂,包括第一代抗组胺剂如阿利马嗪(异丁嗪)、安他唑啉,阿扎他啶、溴马秦、卡比沙明、氯丙嗪、氯马斯汀、氯西尼嗪、赛克利嗪、氯环嗪、赛庚啶、

茶苯海明、二甲茚定、苯海拉明、溴苯海拉明、氯苯海拉明、多西拉敏、羟嗪、美克洛嗪、美吡拉敏[吡拉明]、甲地嗪、奥沙米特、苯茚胺、非尼拉敏、溴苯那敏、氯苯那敏、氟苯那敏、奥芬那君、苯托沙敏、异丙嗪、曲吡那敏和曲普利啶以及它们的类似物和衍生物；

苯二氮䓬类药物，其通过正变构调节$GABA_A$受体来增强γ-氨基丁酸(GABA)对该受体的影响，如阿地唑仑、阿普唑仑、利眠宁、氯马唑仑、氯硝西泮、氯氮卓、地西泮、艾司唑仑、依替唑仑(一种苯二氮䓬类似物)、氟硝西泮、氟西泮、哈拉西泮、氯普唑仑、劳拉西泮、氯羟安定、咪达唑仑、硝甲西泮、硝西泮、奥沙西泮、普拉西泮、夸西泮、替马西泮和三唑仑以及它们的类似物和衍生物；

非苯二氮䓬类药物(也称为Z药物)，其为$GABA_A$受体的正变构调节剂，如β-咔啉类(如阿贝卡奈、吉多卡尔和ZK-93423)、环吡咯酮类(例如，帕戈隆、帕秦克隆、舒普罗酮、舒立克隆、佐匹克隆和右佐匹克隆)、咪唑并吡啶(例如，阿吡坦、奈可吡旦、沙立吡旦和唑吡坦)、吡唑并嘧啶(例如，地伐普隆、法西普隆、茚地普隆、lorediplon、奥西普隆、帕那普隆、他尼普隆和扎来普隆)和三唑并哒嗪(例如，CL-218872)以及它们的类似物和衍生物；

巴比妥类，其为$GABA_A$受体的正变构调节剂，如阿洛巴比妥、异戊巴比妥、阿普比妥、烯丙苯巴比妥、巴比妥类、溴烯比妥、仲丁比妥、甲苯比妥、戊巴比妥、苯巴比妥、司可巴比妥和硫喷妥钠以及它们的类似物和衍生物；

GABA类似物，如加巴喷丁和普瑞巴林以及它们的类似物和衍生物；

褪黑激素受体(例如，MT_1和/或MT_2)激动剂，如褪黑激素、阿戈美拉汀、LY-156735、piromelatine、雷美尔通和他司美琼以及它们的类似物和衍生物；

食欲素受体(例如，OX_1和/或OX_2)拮抗剂，如almorexant、suvorexant、SB-334867、SB-408124、SB-649868、TCS-OX2-29和N-乙基-2-[(6-甲氧基-吡啶-3-基)-(甲苯-2-磺酰基)氨基]-N-吡啶-3-基甲基-乙酰胺(EMPA)以及它们的类似物和衍生物；

4-喹唑酮，如氟喹酮、氯喹酮、二丙喹酮、依他喹酮、mebroqualone、甲氯喹酮、甲喹酮、甲基甲喹酮和硝基喹酮以及它们的类似物和衍生物；

阿片样物质(例如，用于疼痛相关的睡眠障碍)，如丁丙诺啡、可待因、芬太尼、氢可酮、氢吗啡酮、左啡诺、美沙酮、吗啡、乙基吗啡、羟考酮、羟吗啡酮、哌替啶、丙氧芬，右丙氧芬、蒂巴因和曲马多以及它们的类似物和衍生物；

草本植物，如大麻(Cannabis)(包括大麻类，如大麻二酚[CBD]和四氢大麻酚[THC]、皮特尤里树(Duboisia hopwoodi)(皮特尤里树)、啤酒花(Humulus lupulus)(啤酒花)、贯叶连翘(Hypericum perforatum)(圣约翰草)、毒莴苣(Lactuca virosa)(毒莴苣)、薰衣草属(Lavandula)(薰衣草)、德国洋甘菊(Matricaria chamomilla)(洋甘菊)、荆芥(Nepeta cataria)(猫薄荷)、西番莲属(Passiflora)(西番莲)(例如，P.incarnata)、卡瓦胡椒(Piper methysticum)(卡瓦胡椒)、Prostanthera striatiflora(条纹薄荷)、Sceletium tortuosum(kanna)、黄芩属(Scutellaria)(黄芩)(例如，S.canescens、S.cordifolia、S.galericulata和S.lateriflora)、缬草(Valeriana officinalis)(缬草)和睡茄(Withania somnifera)(ashwagandha)；以及

其他类型的物质，如S-腺苷基-L-半胱氨酸、L-色氨酸，L-精氨酸-L-天冬氨酸、δ睡眠诱导肽(DSIP)、水合氯醛、乙醇、2-甲基-2-丁醇、γ-羟丁酸(GHB)、格鲁米特、美托咪啶、右美

托咪啶、异戊酸甲酯(伐力多)、S32212、α_2肾上腺素能激动剂(如可乐定)和碳酸酐酶抑制剂(如乙酰唑胺和托吡酯)以及它们的类似物和衍生物。

[0102] 所述另外的睡眠辅助药剂还可视其治疗促使睡眠困难的病况的能力(例如,不正常的肢体运动或行为)来选择。例如,抗惊厥药可与司洛匹坦组合用于治疗睡眠异常,如不宁腿综合征、周期性肢体运动障碍或夜间进食综合征。抗惊厥药的实例包括但不限于:卡马西平、加巴喷丁、普加巴林、丙戊酸及其盐类(例如,丙戊酸钠)以及其类似物和衍生物。

[0103] 所述另外的睡眠辅助药剂可以任何合适的模式施用。在某些实施方案中,所述另外的睡眠辅助药剂为口服、颊面或舌下施用。

治疗施用与剂量

[0104] 术语"施用(administration of或administering)"化合物应当理解为以一定形式向需要治疗的个体提供本发明的化合物,所述形式可以治疗上有用的形式及治疗有效的量被引入所述个体的体内,包括但不限于口服剂型,如片剂、胶囊、糖浆、悬浮液等。

[0105] 术语"治疗(treat、treating和treatment)"慢性瘙痒均是指降低急性或慢性瘙痒症状的频率(包括将其整个消除)、避免急性或慢性瘙痒的发生和/或减轻急性或慢性瘙痒症状的严重程度。

[0106] 术语"治疗有效量"是指足够量的本发明的化合物,在合适的组合物中并以合适的剂型用来治疗所关注的疾病病况。"治疗有效量"将随化合物、引发瘙痒的病况的严重程度以及待治疗患者的年龄、体重等而变化。

[0107] 术语"负荷剂量"是指本发明的化合物或组合物的量,其常常大于后续剂量,出于建立药物治疗水平的目的而施用。更一般地说,负荷剂量是化合物I或其药学上可接受的盐、溶剂合物或多晶型物的量,其于显现(presentation)后一段时间但在一个或多个维持剂量开始前向患有瘙痒的患者施用。或者,负荷剂量是指一个或一系列剂量,其可在治疗开始时给予以使活性成分迅速达到目标浓度。

[0108] 治疗瘙痒的本方法需要向有此类治疗需求的患者施用司洛匹坦或含有司洛匹坦的药物组合物。优选口服施用所述化合物和/或药物组合物。已知各种递送体系(例如,封装于脂质体、微粒、微胶囊、胶囊等中)可用于施用司洛匹坦化合物和/或组合物。所述化合物和/或药物组合物可通过持续释放剂型来递送。

[0109] 能有效治疗患者的瘙痒的司洛匹坦或其药学上可接受的盐、溶剂合物或多晶型物的量将取决于病况的具体性质,并且可由本领域已知的标准临床技术确定。另外,可任选地采用体外或体内测定来帮助确定最佳剂量范围。任何具体个体的具体剂量水平将取决于多种因素,包括组合物的活性、年龄、体重、一般身心健康状况、遗传因素、环境影响、性别、膳食、施用时间、施用途径、排泄率以及所治疗的瘙痒的严重程度。

[0110] 优选地,所述剂型适于一天三次、两次或一次向患者施用。更优选地,每天一次地施用治疗有效量。或者,可以隔天、每三天、每四天或一周一次给药。在一些实施方案中,遵循长期给药方案施用司洛匹坦(serlopitant)。在某些实施方案中,在至少2周、3周、1个月、1.5个月、2个月、3个月、4个月、5个月、6个月或更长的时间段上施用治疗有效量的司洛匹坦。

[0111] 患者可在任何方便的时间给药。然而,可在临睡前服用一日剂量以使副作用(如头晕或嗜睡)最小化。在用于治疗瘙痒以外用途的人临床试验中,NK-1受体拮抗剂已被证明会

引起嗜睡。例如,Ratti等人报道了在采用卡索吡坦治疗重度抑郁症的患者中,其嗜睡发生率是采用安慰剂的两倍之多(J.Clin.Psychopharmacol.,2011,31:727-733)。在类似的临床试验中也观察到嗜睡,该试验是测试NK-1受体拮抗剂L-759274作为抗抑郁药(M.S.Kramer等人,Neuropsychopharm.,2004,29:385-392)。因此,在本发明的一个实施方案中,于患者睡觉前施用司洛匹坦。

[0112] 可以单独或与其它药物组合给药,并可持续有效治疗瘙痒所需的时间。例如,本发明的化合物可与另一种物质组合施用,所述另一种物质对速激肽具有互补作用,而对本发明的P物质具有抑制作用。适当的化合物包括其它NK-1受体拮抗剂如,但不限于,卡索吡坦(GW679769)、L-759274、L-733060、CP122721、BIIF1149CL、DNK333、M516102、依洛匹坦、罗拉吡坦、奥维匹坦、LY-686017、拉奈匹坦(LY-303870)、maropitant、维替匹坦、沃氟匹坦、阿瑞吡坦、福沙吡坦、AV-818和TA-5538。

[0113] 本发明的化合物用于口服施用的剂量范围可以施用的药量/时段来表述。一定量的活性成分可以根据上述因素适当地以一天一次或多次给药。例如,可以一天一次、一天两次、一天三次、一天四次或更多次给予。合适的剂量范围为约0.1mg至约30mg,并且优选地,约1mg至约7.5mg。合适的剂量通常为一天一次或多次0.10mg、0.15mg、0.20mg、0.25mg、0.5mg、0.75mg、1mg、2mg、2.5mg、3mg、4mg、5mg、6mg、7mg、8mg、9mg、10mg、15mg、20mg、25mg、30mg、35mg、40mg、50mg、100mg或200mg。优选地,一天一次施用0.25mg、1mg或5mg的剂量。

[0114] 或者,用于口服施用的本发明的化合物的合适的剂量范围通常为约0.001mg至约500mg药物/千克体重、优选约0.1mg至约200mg药物/千克体重、并更优选约1至约100mg/kg体重/天。可以由本领域技术人员已知的方法容易地确定剂量范围。活性成分的量(例如其可以与载体材料组合以生成单个剂型)将随所治疗的患者和具体的施用模式而变化。单位剂型通常将包含约0.25mg至约500mg的活性成分。

[0115] 在需要活性药物持续更长时间的情况下,例如但不限于,在治疗慢性瘙痒时,采用这样的给药时间表,其中在施用负荷剂量后,如本领域技术人员确定适当的,施用(i)一个或多个第二负荷剂量,以及一个(或多个)维持剂量,或(ii)一个或多个维持剂量,不施用第二负荷剂量。所述负荷与维持剂量的施用时间表可基于具体患者的个体需求而定。在本发明的一个实施方案中,施用一个负荷剂量,然后在适当的间隔后(如一天后)施用治疗有效的维持剂量。在另一个实施方案中,于第1天施用负荷剂量,第2天施用第二负荷剂量,并在第3天及之后的治疗持续时期施用维持剂量。负荷剂量可以是维持剂量的五倍、四倍、三倍或两倍。优选地,负荷剂量为维持剂量的三倍。可以任何合适的模式(例如,口服)施用所述活性药物。

确定疗效

[0116] 可在本领域技术人员已知的瘙痒实验动物模型中测试本发明组合物的有效性。例如,各种小鼠模型已被用于评价对瘙痒的治疗。Tsukumo等人描述了一个模型,其中在BALB/c小鼠中4-乙氧基亚甲基-2-苯基-2-噁唑啉-5-酮(噁唑酮)诱导具有相关瘙痒反应的慢性皮炎,其可用于确定止痒治疗是否有效(J.Pharmacol.Sci.,2010,113:255-262)。Costa等人报道了类似模型,其中Phoneutria nigriventer蜘蛛毒液被用作瘙痒诱导物(Vascul.Pharmacol.,2006,45(4):209-14)。类似地,Ohmura等人使用苦基氯在NC/Nga小鼠中刺激抓挠行为(Eur.J.Pharmacol.,2004;491:191-194)。基本上,采用刺激剂在受试动物

中诱发瘙痒，施用测试化合物或安慰剂，并在受控制的情况下观察动物。使用标准统计技术对抓挠行为进行定量和分析。如果持续的或严重的抓挠得到抑制，则认为测试化合物是有效的。

[0117] 本发明的方法和组合物在治疗急性和慢性瘙痒中的功效还可以任选地在遵循美国食品药品管理局(FDA)所规定的适当标准与道德准则情况下所进行的人临床试验中得到评价。当药物的总体安全性由在健康志愿者中进行的I期临床试验所确定后，在具有治疗的病况的患者中进行评估该药物的安全性与功效的II期试验。通常，此类试验是双盲并安慰剂对照的，并且可以是剂量范围的(dose-ranging)。通过研究不同群体和不同剂量以及通过将该药物与其它药物组合使用，在III期研究中收集更多有关安全性和有效性的信息。

[0118] 由于瘙痒的改善经受患者的个人知觉，所以很难以典型的临床终点来评价。然而，已经创建了两种标准化的评估工具并可用于证实本发明的实用性的临床试验。视觉模拟评分(VAS)是评价瘙痒强度最常用的工具(N.Q.Phan等人，Acta Derm.Venereol.，2012;92:502-507)。VAS是有着100-mm水平线的图形工具，其左端标记为“无症状”而右端标记为“可想到的最坏症状”。患者被要求在对应于症状强度的点上画一条竖线以标示水平刻度。以毫米计测量从左端到患者所作竖直标记的长度。百分之一的分隔被认为是足够灵敏的(R.C.Aitken，Proc.R.Soc.Med.，1969，62:989 993)。可使用本领域技术人员已知的标准统计技术分析该结果。

[0119] 除VAS以外，皮肤病生活质量指数(DLQI)可用于评价慢性瘙痒治疗的功效。DLQI，一种皮肤病生活质量的自填式一般性问卷，最初由University Hospital of Wales的一家皮肤病诊所开发并发表(A.Y.Finlay与G.K.Khan，Clin.Exper.Derm.，1994，19:210-216)。独立研究已经证实DLQI是一种用于评估皮肤病患者生活质量的简单有效的方法(H.B.Hahn等人，J.Am.Acad.Dermatol.，2001，45(1):44-8)。这份简单的、十个问题确认的问卷的现行版，连同使用和打分说明，可得自School of Medicine，Cardiff University，Wales，UK(万维网URL dermatology.org.uk/quality/)。

[0120] 以举例说明而非限制的方式提供以下实施例。

实施例

[0121] 以下实施例中所有非活性药物成分均符合美国药典和美国药品集的规定并根据USP/NF纲要中所指明的各成分的专题进行测试和释放。

实施例1.制备司洛匹坦片剂

[0122] 司洛匹坦，3-[(3aR，4R，5S，7aS)-5-[(1R)-1-[3，5-双(三氟甲基)苯基]乙氧基]-4-(4-氟苯基)-1，3，3a，4，5，6，7，7a-八氢异吲哚-2-基]环戊-2-烯-1-酮(化合物1)可被配制成片剂用于口服使用。表1示出了示范性剂量的定性/定量组成。在药物开发过程中，赋形剂的量可发生微小变化(+/-10％)。

表1

组分	功能	组合物的%
化合物1	活性剂	1-6 %
微晶纤维素	稀释剂	50-60%
甘露醇	稀释剂	20-30%
交联羧甲基纤维素钠	崩解剂	1-3%
胶态二氧化硅	崩解剂	0.25-0.5%
月桂基硫酸钠	表面活性剂	5-6%
硬脂酸镁	润滑剂	0.25-2%
总片剂组合物		100%

[0123] 0.25、1和5mg的片剂效力被制备成压片制剂。片剂制造方法对所有提出的效力是一样的。该方法由以下步骤组成:1)将化合物1、甘露醇以及月桂基硫酸钠混合;2)将剩下的甘露醇加入搅拌机并混合;3)将微晶纤维素、交联羧甲基纤维素钠和胶态二氧化硅加入包含以上混合物的搅拌机以完成混合并将混合物去聚集(如有必要);4)使用之前已经过筛选(如有必要)的硬脂酸镁润滑该混合物;5)碾压和研磨经过润滑的混合物,然后用之前已经过筛选(如有必要)的硬脂酸镁润滑;以及6)然后将该混合物压制成适当重量的片剂。

实施例2.制备司洛匹坦胶囊

[0124] 司洛匹坦(化合物1)还可作为装满液体的胶囊被供应给诊所。表2示出了示范性剂量的定性/定量组成。在药物开发过程中,赋形剂的量可发生微小变化(+/-10%)。

表2

组分	功能	单位强度		
		0.25 mg	1 mg	4 mg
胶囊填充物				
化合物 1	活性剂	0.25 mg	1 mg	4 mg
甘油单酯和甘油二酯	增溶剂	399 mg	398.6 mg	395.6 mg
丁基化羟基苯甲醚	抗氧化剂	0.40 mg	0.40 mg	0.40 mg
胶囊外壳				
#0 白色不透明硬明胶胶囊*	胶囊外壳	96 mg**	96 mg**	96 mg**
明胶***	束带(Banding)组分	---	---	---
聚山梨醇酯 80***	束带组分	---	---	---

*胶囊由Capsugel(Morristown,NJ)提供并含有明胶和二氧化钛

**空胶囊外壳的大致重量

***密封胶囊外壳所需的

[0125] 通过将药物溶解在甘油单酯和甘油二酯中来制备所述制剂。此外，加入0.1重量%的丁基化羟基苯甲醚作为抗氧化剂。将初始胶囊强度分配到硬明胶胶囊中并喷洒1:1(重量/重量)的水:乙醇溶液进行密封。将后续效力(包括0.25、1和4mg)分配到硬明胶胶囊中并用明胶/聚山梨醇酯80条带密封。以类似方式制备对应的安慰剂制剂，但不添加药物和抗氧化剂。

[0126] 胶囊制造方法对所有效力是一样的。该方法由以下步骤组成:1)在40℃熔化甘油单酯和甘油二酯赋形剂(如有必要);2)将所述甘油单酯和甘油二酯加入适当尺寸、夹套的容器中并开始混合;3)将丁基化羟基苯甲醚加入所述甘油单酯和甘油二酯并混合直至溶解(最少10min);4)将化合物1缓慢加入到该混合物中并混合直至溶解(视觉确认);5)将该溶液填充至硬明胶胶囊中;6)用明胶和聚山梨醇酯80的混合物密封该填充好的胶囊;7)让密封好的胶囊干燥过夜并然后目视检查胶囊有无泄漏;8)将可用的胶囊称重分拣(如有必要);以及9)然后将成品用适合的容器包装。

实施例3.司洛匹坦在慢性瘙痒中的临床研究

[0127] 根据ICH的良好临床实践的指导方针、美国联邦法规、健康保险携带与责任法案(HIPAA)以及任何地方性监管要求，进行测试三种剂量的司洛匹坦在治疗慢性瘙痒中的功效的良好可控的人临床试验。该研究为II期的随机、双盲、平行分组、安慰剂对照、多中心试验，设计用于在患有慢性瘙痒的患者中测试司洛匹坦的若干剂量相对于安慰剂的有效性和安全性。该研究的患者群体包括成年人、男性或女性、18至72岁。所述患者必须之前被确诊患有由任何病因(除了尿毒症、肝衰竭、癌症或癌症治疗)引起的慢性瘙痒，所述慢性瘙痒被

定义为瘙痒大于6周并且VAS分数大于7。

[0128] 让患者随机接受安慰剂或活性剂的三种剂量中的一种。患者在总共的2至8周内每日一次口服活性药物或安慰剂。每位主体的最长研究持续时间为大约14周，并且包括最长达2周的筛选期、2-8周的治疗期以及最长达4周的随访期。该研究的参数汇总于表3中。

表3

研究题目:	司洛匹坦在慢性瘙痒患者中的 II 期研究
进展阶段:	II 期
研究目标:	确定剂量、效力和安全性
研究设计:	多中心、双盲、平行分组、确定剂量
样本大小:	80-240 名可评价用于分析的主体
研究群体:	患有慢性瘙痒（6 周以上的持续期）的、对标准治疗无应答的患者
研究产品:	每日口服片剂
	剂量和频率: 第 1 天: 3 倍药物剂量（0.25 mg、1 mg 或 5 mg）的负荷剂量，然后是药物 A、药物 B 或药物 C 药物 A: 0.25 mg 司洛匹坦/天，2 至 8 周 药物 B: 1 mg 司洛匹坦/天，2 至 8 周 药物 C: 5 mg 司洛匹坦/天，2 至 8 周
参考产品:	无
对照产品:	匹配的安慰剂/天，2 至 8 周
效力评价标准:	每天通过患者日记对效力进行测量。患者在 10 分的 VAS 量表上记录瘙痒水平。通过活性剂与安慰剂之间 VAS 分数的变化来测量临床反应。次要终点将包括测量皮肤病生活质量指数（DLQI）、损伤愈合以及患者与医生整体评估。
安全性评价标准:	对研究人员所观察到的或得到报告的所有局部的和全身的不良事件进行评价。就强度、持续时间以及与研究产品的因果关系，对所有不良事件进行评价。
统计方法:	主要研究终点是安慰剂与活性剂之间 VAS 分数在基线与治疗上的差异。
研究地点:	多中心

[0129] 可进行依据相似设计的额外的临床试验以测试活性成分的不同剂量水平或区分最佳剂量或给药时间表。另外，药物在特定群体(如老人、儿童或患有尿毒症、肝衰竭、癌症的患者或正接受癌症治疗的患者)中的效力可在以相似方式实施的额外的临床试验中得到确定。

实施例4.包含司洛匹坦的局部制剂

[0130] 表5示出了各种包含司洛匹坦的局部制剂。所述制剂包含Vanicream™ Moisturizing Skin Cream(“VM”)、Vanicream™ Lite Lotion(“VLL”)或Aquaphor® Healing Ointment(“AP”,来自Eucerin)作为基质(base)或载体。VM和VLL是水包油乳状液,而AP具有油基质。在乙醇(EtOH)中的无基质司洛匹坦(化合物1或“Cpd1”)原液是通过以下制备的:将无基质司洛匹坦最大限度地溶解于乙醇中并然后通过具有0.02微米孔径的Anotop®25无机过滤器过滤所得溶液。无基质司洛匹坦在乙醇中的最大溶解度为64.5mg/g EtOH或6.45%w/w。为制备局部制剂,将所述司洛匹坦/乙醇原液加入包含特定量基质的配衡管中直至所得混合物称重为25.0g。使用振动台用力混合该混合物2分钟并然后缓慢旋转4天。对于“C”制剂而言,加入不含司洛匹坦的乙醇使得“B”和“C”制剂将含有相同量的基质和乙醇。

表5

混合物	批量(g)	基质(g)	Cpd 1/EtOH原液 (g)	空白EtOH(g)	% Cpd 1 (w/w)	% EtOH (w/w)
VM-A	25.0	23.06	1.94	0.0	0.5	7.8
VM-B	25.0	21.12	3.88	0.0	1.0	15.5
VM-C	25.0	21.12	1.94	1.94	0.5	15.5
VLL-A	25.0	23.06	1.94	0.0	0.5	7.8
VLL-B	25.0	21.12	3.88	0.0	1.0	15.5
VLL-C	25.0	21.12	1.94	1.94	0.5	15.5
AP-A	25.0	23.06	1.94	0.0	0.5	7.8
AP-B	25.0	21.12	3.88	0.0	1.0	15.5
AP-C	25.0	21.12	1.94	1.94	0.5	15.5

[0131] AP被确定为不适合用作包含司洛匹坦的乙醇溶液的基质,因为乙醇不溶于该基质。在与15.5%乙醇混合4天后,VM基质在15x显微放大下显得稳定/无变化。在与15.5%乙醇混合4天后,VLL基质在15x显微放大下显示出一些层状结构的聚集,但该基质的整体变化甚微。可例如,针对司洛匹坦的皮肤渗透,来测试VM和VLL制剂。

实施例5.局部制剂中司洛匹坦的体外皮肤渗透

[0132] 用于体外皮肤渗透研究的局部制剂A-D示于表6中。在实施例4中描述了制剂A-D的基质“VM”和“VLL”。根据实施例4中所述的程序制备了制剂A-D。

表6

制剂（基质）	最终质量（g）	基质（g）	Cpd 1/EtOH 原液（g）	空白 EtOH（g）	% Cpd 1（w/w）	% EtOH（w/w）
A（VM）	25.28	21.27	0.0	4.01	0.0	15.9
B（VLL）	25.12	21.19	3.93	0.0	1.0	15.6
C（VM）	13.80	11.63	2.17	0.0	1.0	15.7
D（VLL）	25.02	21.15	0.0	3.87	0.0	15.5

[0133] 使用Franz扩散池评价了局部制剂A-D中司洛匹坦的体外皮肤渗透。图2说明了Franz扩散池。设置具有4.15cm^2圆形渗透面积和19mL接收室体积的Franz扩散池以及用于将温度保持在37℃的热调节外水夹套。所述接收室填充有包含10％乙醇与1％Tween®80的19mL 1×PBS(pH 7.5)。溶解度测试表明：在37℃温育1小时后，司洛匹坦在0.5、5和50ug/mL的浓度下保持可溶于此溶液中。如果未使用Tween®80，司洛匹坦的溶解度显著降低，而如果未使用乙醇，司洛匹坦的溶解度略有下降。

[0134] 人皮肤经预处理去除所有的皮下脂肪并在使用前用70％乙醇清洗。通过目视检查确保所述皮肤没有任何表面不规则或小洞并将其等分成四片。将所述皮肤角质层面朝上固定在所述接收室上。将约100mg局部制剂A、B、C或D应用于皮肤上(实际重量：A，103.8mg；B，101.3mg；C，103.2mg；以及D，103.8mg)，然后盖上封口膜以避免蒸发。

[0135] 在0.5、1、2、4、6、18和22小时，通过Franz扩散池的取样口抽取约0.5mL溶液。在每次取样后，向所述接收室补充等体积的新鲜扩散缓冲液。在实验结束时(经过22小时温育)，用甲醇擦净所述皮肤，并对经制剂处理过的区域进行称重并冷冻用于冰冻切片。

[0136] 所有的样品在LC-MS/MS分析前均通过固相萃取(SPE)处理。简而言之，具有30mg吸附剂质量/1mL体积的Strata-X 33um聚合物反相柱(Phenomenex)经1mL甲醇调节并用1mL水平衡。将300uL样品上样到该柱，然后用1mL 30％甲醇清洗。用乙腈中的2％甲酸来洗脱司洛匹坦。该样品然后通过氮气吹干而浓缩并重悬浮于50uL 50％甲醇中。首先通过向扩散缓冲液中掺入已知浓度的司洛匹坦来生成工作标准品，然后使用同样的SPE方法对其进行处理。达到0.1ng/mL的灵敏度。通过与标准品比对来确定得自制剂A-D的样品中司洛匹坦的浓度。正如所预期的，在得自局部制剂A和D的样品中，未检测到司洛匹坦。图3示出了在0.5、1、2、4、6、18和22小时处，从局部制剂B和C向接收室的司洛匹坦的累积释放。经过初始滞后，于6小时在接收室中由LC-MS/MS检测到司洛匹坦。图3表明在此项体外研究中，相比局部制剂C，局部制剂B导致了司洛匹坦经皮肤更强的渗透。

[0137] 在实验结束时确定保留在皮肤中的司洛匹坦的量。擦拭所述皮肤并用甲醇清洗。用恒冷箱将经制剂处理过的区域切成25um的水平切片。将每10份切片合并置于Eppendorf管中，称重并用两倍体积的1mg/mL释放酶在37℃消化1小时。用探头超声波破碎仪令消化后的皮肤切片进一步均质化。向25uL所述皮肤匀浆中加入25uL 50％甲醇和100uL乙腈/甲醇以提取司洛匹坦。对于掺入的标准品而言，向25uL空白皮肤匀浆中加入溶于50％甲醇中的25uL司洛匹坦溶液(从5ng/mL至5000ng/mL)，然后加入100uL乙腈/甲醇。提取出的司洛匹坦

由LC-MS/MS定量。图4示出了实验结束时保留在皮肤中的司洛匹坦(在图4中称为“VPD737”)的量。每根柱表示在250um皮肤层中,ug司洛匹坦/g皮肤。对于局部制剂B和C各自而言,所述柱从左到右表示保留在皮肤层(从角质层到真皮)中的司洛匹坦的量。

实施例6.代表性的包含司洛匹坦的局部制剂

[0138] 表7提供了局部制剂的非限制性实例,所述制剂可由司洛匹坦或其盐、溶剂合物或多晶型物以及任选另外的治疗剂制备。

表7

剂型	除司洛匹坦以外的成分
霜剂	山梨醇、鲸蜡醇、肉豆蔻酸异丙酯、硬脂酸甘油酯、PEG-100硬脂酸酯、矿脂、苯甲醇、二氧化钛和水

霜剂	丙二醇、十八十六醇、Cremophor®A6、Cremophor®A25、液体石蜡、对羟基苯甲酸酯和水
霜剂	甘油、山梨醇、棕榈酸异丙酯、乳化蜡、苯甲醇、pH 调节剂（如 NaOH 或乳酸）和水
霜剂	甘油、硬脂酸、单硬脂酸甘油酯、三乙醇胺、对羟基苯甲酸酯和水
霜剂	丙二醇、十八十六醇、矿物油、白矿脂、鲸蜡硬脂醇聚醚-30、氯甲酚、磷酸二氢钠、磷酸、水和任选 NaOH
霜剂	甘油、十八十六醇、矿物油、矿脂、鲸蜡醇聚醚-20、双咪唑烷基脲、二氯苯甲醇、乙二胺四乙酸（EDTA）、乙二胺四乙酸二钠、磷酸氢二钠和水
霜剂	丙二醇、硬脂醇、白矿脂、聚山梨酯 60、对羟基苯甲酸酯和任选水
霜剂	丙二醇、硬脂醇、鲸蜡醇、油醇、甘油单、二或三酯，鲸蜡硬脂醇硫酸酯钠、苯甲醇、柠檬酸、pH 调节剂（如 NaOH 或乳酸）和水
霜剂	己二醇、硬脂醇、丙二醇硬脂酸酯、白腊、白矿脂、淀粉辛烯基琥珀酸铝、鲸蜡硬脂醇聚醚-20、二氧化钛、磷酸和水
霜剂	丙二醇、山梨醇、单异硬脂酸甘油酯、聚甘油-3 油酸酯、矿物油、微晶蜡、胶质二氧化硅、对羟基苯甲酸酯、EDTA 或乙二胺四乙酸二钠和水
霜剂	丙二醇、硬脂酸、棕榈酸异丙酯、乳化蜡、蜂蜡、聚山梨酯 60、抗氧化剂（如没食子酸丙酯）、防腐剂（例如，山梨酸和山梨酸钾）、pH 调节剂（如 NaOH 和/或柠檬酸）和水
霜剂	十八十六醇、羊毛脂醇、肉豆蔻酸异丙酯、硬脂酸铝、硬脂酸镁、矿物油、白矿脂、水和任选乙二胺四乙酸二钠和/或乳酸
霜剂	丙二醇、十八十六醇、白软石蜡、液体石蜡、羊毛脂、西甲硅油 M30、Tween®60、对羟基苯甲酸酯和水
霜剂	十八十六醇、矿物油、白矿脂、鲸蜡醇聚醚-20、对羟基苯甲酸酯、柠檬酸、柠檬酸钠和水

霜剂	丙二醇、十八十六醇、聚氧乙烯 20 十六烷基-十八烷基醚、矿物油（液体石蜡）、矿脂（白软石蜡）、氯甲酚、对羟基苯甲酸酯、磷酸二氢钠和水
霜剂	丙二醇、十八十六醇、硬脂酸、棕榈酸鲸蜡酯、失水山梨醇单硬脂酸酯、矿物油、聚山梨酯 60、苯甲醇和水
软膏	己二醇、丙二醇硬脂酸酯、白腊、白矿脂、磷酸和水
软膏	丙二醇、矿物油、矿脂、硬脂醇聚醚-2、生育酚、EDTA 或乙二胺四乙酸二钠、磷酸氢二钠和水
软膏	丙二醇、脂肪醇柠檬酸酯、脂肪酸季戊四醇酯，失水山梨醇倍半油酸酯、白矿脂、蜂蜡、硬脂酸铝、丁基羟基茴香醚（BHA）、柠檬酸和任选水
软膏	醇（如乙醇或丙二醇）、聚乙烯或白矿脂、矿物油和任选水
凝胶	乙醇、卡波姆 934P、三乙醇胺和水
凝胶	甘油、卡波姆 940、泊洛沙姆、二甲硅油、月桂醇磺基琥珀酸酯二钠、二氧化硅、防腐剂（如过氧化苯甲酰和/或对羟基苯甲酸甲酯）、EDTA 或乙二胺四乙酸二钠、pH 调节剂（如 NaOH 或乳酸）和水
凝胶	甘油、羟基-β-环糊精、羟乙基纤维素、对羟基苯甲酸酯、EDTA 或乙二胺四乙酸二钠和水
凝胶	丙二醇、聚丙烯酸、中链甘油三酯、卵磷脂、聚山梨酯 80、防腐剂（如苯甲酸）、EDTA 或乙二胺四乙酸二钠、pH 调节剂（如 NaOH 或乳酸）和水
凝胶	乙醇、肉豆蔻酸异丙酯、卡波姆 940、三乙醇胺、多库酯钠、EDTA 或乙二胺四乙酸二钠和水
凝胶	丙二醇、Carbopol®941、PEG 400、对羟基苯甲酸甲酯、pH 调节剂（如 NaOH 或乳酸）和水
凝胶	丙二醇、PEG 400、卡波姆 934P、尿囊素、对羟基苯甲酸甲酯、pH 调节剂（如 NaOH 或乳酸）和水
凝胶	醇（如乙醇和/或丙二醇）、卡波姆、磺基琥珀酸二辛酯钠、防腐剂（如过氧化苯甲酰）、pH 调节剂（如 NaOH 或乳酸）和水

凝胶	甘油、丙二醇、芦荟胶、双咪唑烷基脲、辛基/己基酰胺丙基甜菜碱(capryl/capramidopropyl betaine)、对羟基苯甲酸酯、柠檬酸、柠檬酸钠和水
凝胶	乙醇、羟丙基纤维素和水
洗剂	甘油、硬脂醇、硬脂酸甘油酯、PEG-100硬脂酸酯、PEG 400、卡波姆941、环甲基硅油、轻质矿物油、硬脂醇聚醚-21、苯甲醇、山梨酸、山梨酸钾、pH调节剂（如NaOH或乳酸）和水
洗剂	异丙醇、丙二醇、羟丙基纤维素、磷酸二氢钠、磷酸和水
洗剂	丙二醇、鲸蜡醇、硬脂醇、硬脂酸甘油酯、失水山梨醇单硬脂酸酯，轻质矿物油、月桂醇硫酸钠、对羟基苯甲酸酯、EDTA或乙二胺四乙酸二钠、水和任选pH调节剂（如NaOH或柠檬酸）
洗剂	甘油、十八十六醇、异硬脂醇、硬脂酸、硬脂酸甘油酯、月桂酰肌氨酸钠、对羟基苯甲酸甲酯和水
栓剂	醇（如乙醇和/或丙二醇）和饱和脂肪酸的甘油酯
栓剂	95%乙醇和Suppocire®AM（含饱和C_8-C_{18}脂肪酸甘油三酯的甘油酯基质）
拭子	异丙醇、丙二醇和水
泡沫	乙醇、丙二醇、鲸蜡醇、硬脂醇、聚山梨酯60、KOH和水，并由丙烷/丁烷推进剂加压
喷雾（皮肤）	乙醇、十一碳烯酸、肉豆蔻酸异丙酯、月桂基硫酸钠和水
喷雾（皮肤）	甘油、乳糖、十八十六醇、矿物油、鲸蜡醇聚醚-20磷酸酯、磷酸二鲸蜡酯、尿素、磷酸二氢钾、对羟基苯甲酸脂、pH调节剂（如NaOH或乳酸）和水
喷雾（鼻腔）	微晶纤维素、羧甲基纤维素钠、葡萄糖、聚山梨酯80、乙二胺四乙酸二钠、山梨酸钾、pH调节剂（如HCl）、水和任选醇（如乙醇）
喷雾（鼻腔）	微晶纤维素、羧甲基纤维素钠、葡萄糖、聚山梨酯80、苯扎氯铵、苯乙醇、水和任选醇（如乙醇）
喷雾（鼻腔）	羟丙甲纤维素、苯扎氯铵、NaCl、EDTA、柠檬酸、磷酸氢二钠、水和任选醇（如乙醇）

[0139] 本说明书中提及的所有出版物和专利申请均通过引用并入本文，其程度如同每个

单独的出版物或专利申请被明确并单独指明通过引用并入。

[0140] 由上述内容应当理解，尽管出于说明目的在本文中已对本发明的特定实施方案进行了描述，仍然可在不偏离本发明的精神和范围的情况下做出各种修改。因此，本发明不受除所附权利要求书之外的限制。

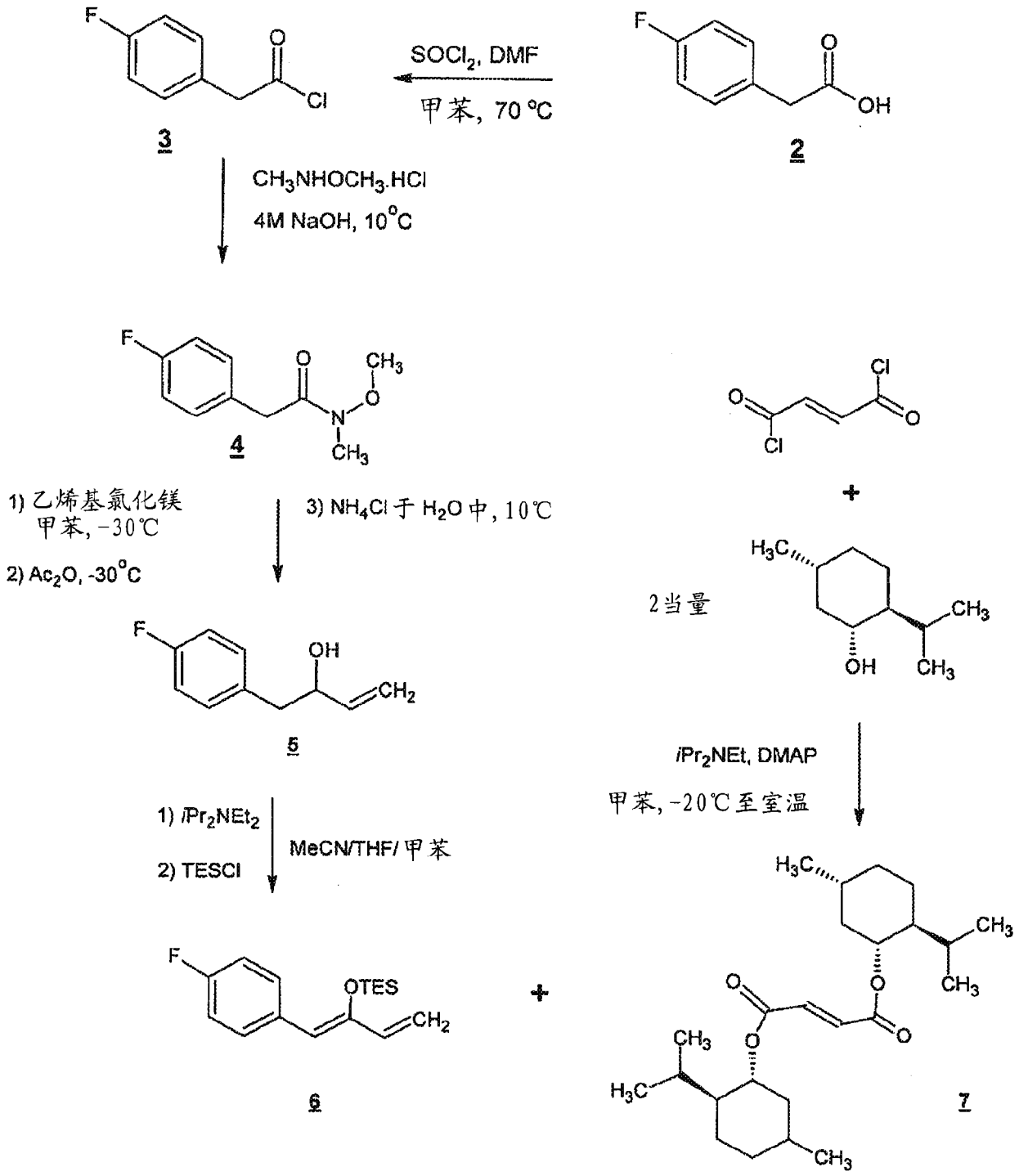

F
O
Cl
3
SOCl2, DMF
甲苯, 70 ℃
F
O
OH
2
CH3NHOCH3.HCl
4M NaOH, 10°C
F
O
CH3
O
N
CH3
4
1) 乙烯基氯化镁
甲苯, -30℃
2) Ac2O, -30°C
3) NH4Cl 于 H2O 中, 10℃
F
OH
CH2
5
1) iPr2NEt2
2) TESCl
MeCN/THF/甲苯
F
OTES
CH2
6
+
Cl
O
O
Cl
+
2当量
H3C
CH3
OH
CH3
iPr2NEt, DMAP
甲苯, -20℃至室温
H3C
CH3
O
O
O
O
CH3
H3C
O
CH3
7

图1

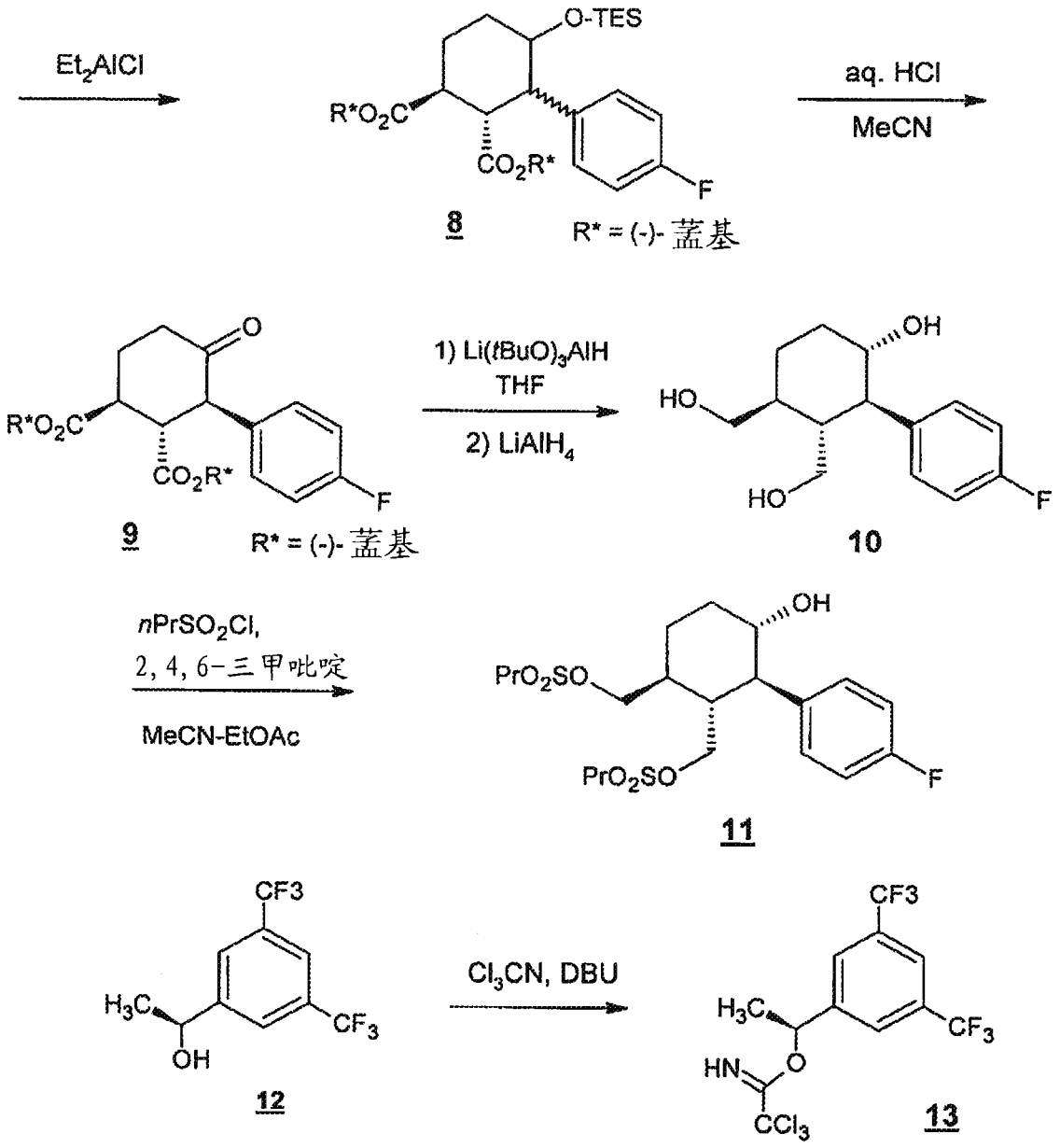

Et2AlCl
O-TES
R*O2C
CO2R*
F
8
R* = (-)-蓋基
aq. HCl
MeCN
O
R*O2C
CO2R*
F
9
R* = (-)-蓋基
1) Li(tBuO)3AlH
THF
2) LiAlH4
OH
HO
HO
F
10
nPrSO2Cl,
2, 4, 6-三甲吡啶
MeCN-EtOAc
OH
PrO2SO
PrO2SO
F
11
CF3
H3C
CF3
OH
12
Cl3CN, DBU
CF3
H3C
CF3
HN
O
CCl3
13

图1(续)

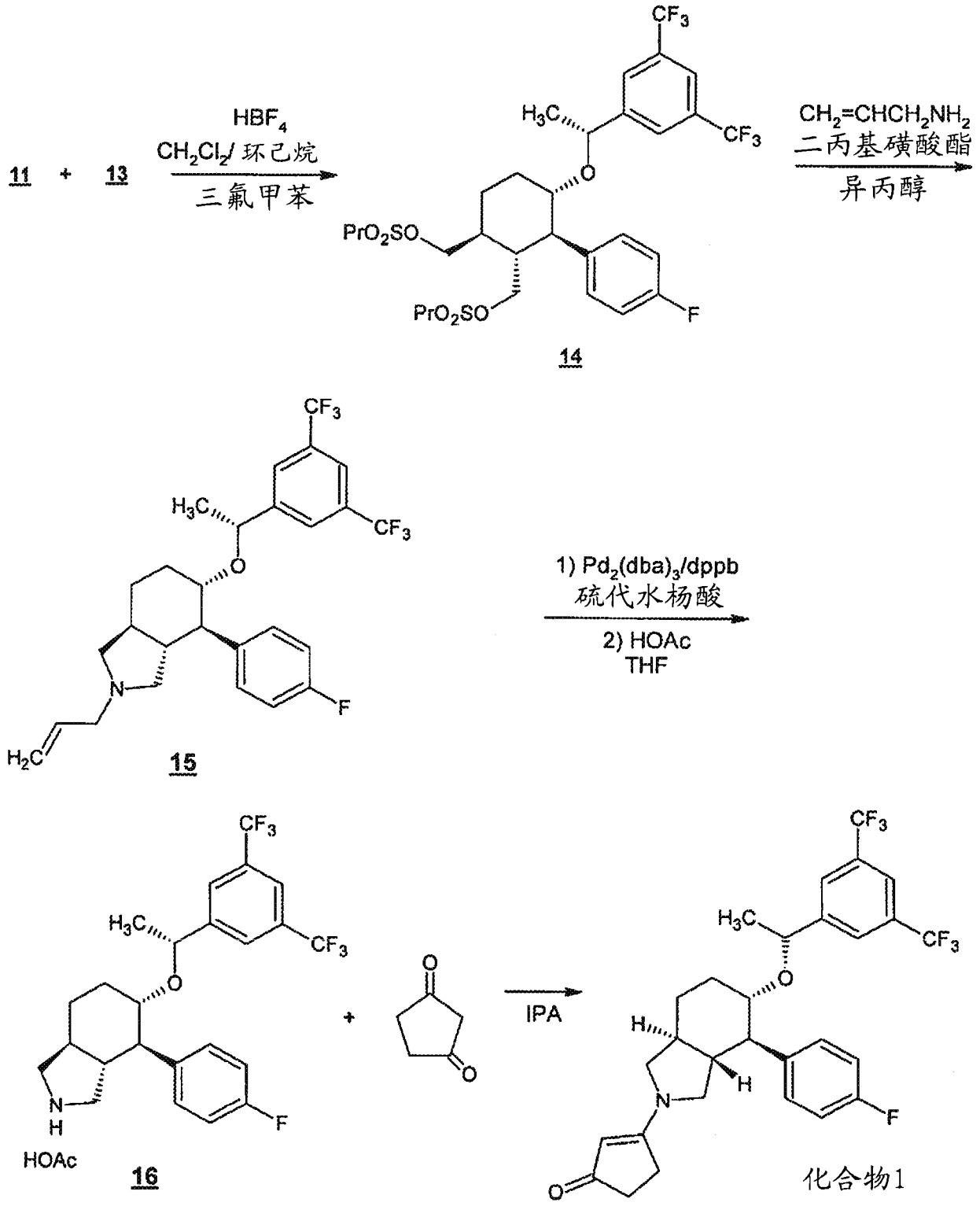

11 + 13
HBF4
CH2Cl2/ 环己烷
三氟甲苯
CH2=CHCH2NH2
二丙基磺酸酯
异丙醇
14
1) Pd2(dba)3/dppb
硫代水杨酸
2) HOAc
THF
15
16
HOAc
IPA
化合物1

图1(续)

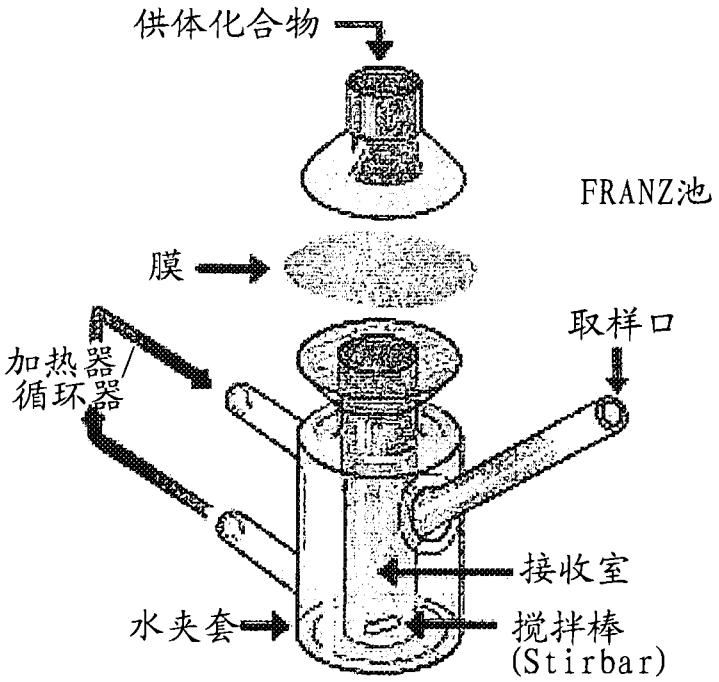

供体化合物
FRANZ池
膜
取样口
加热器/
循环器
接收室
水夹套
搅拌棒
(Stirbar)

图2

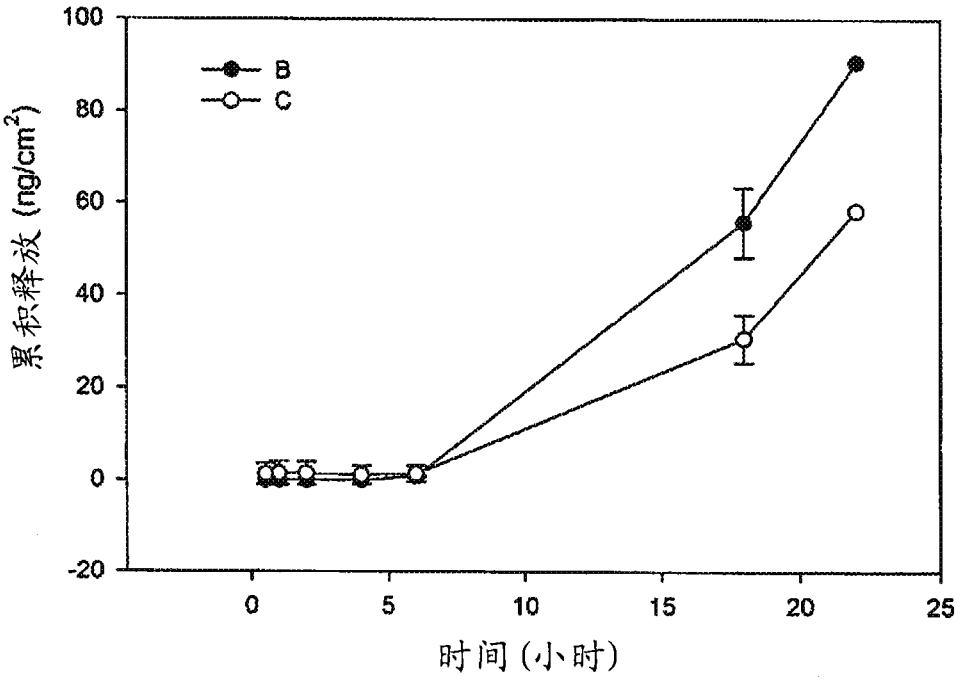

B
C
累积释放 (ng/cm²)
100
80
60
40
20
0
-20
0
5
10
15
20
25
时间 (小时)

图3

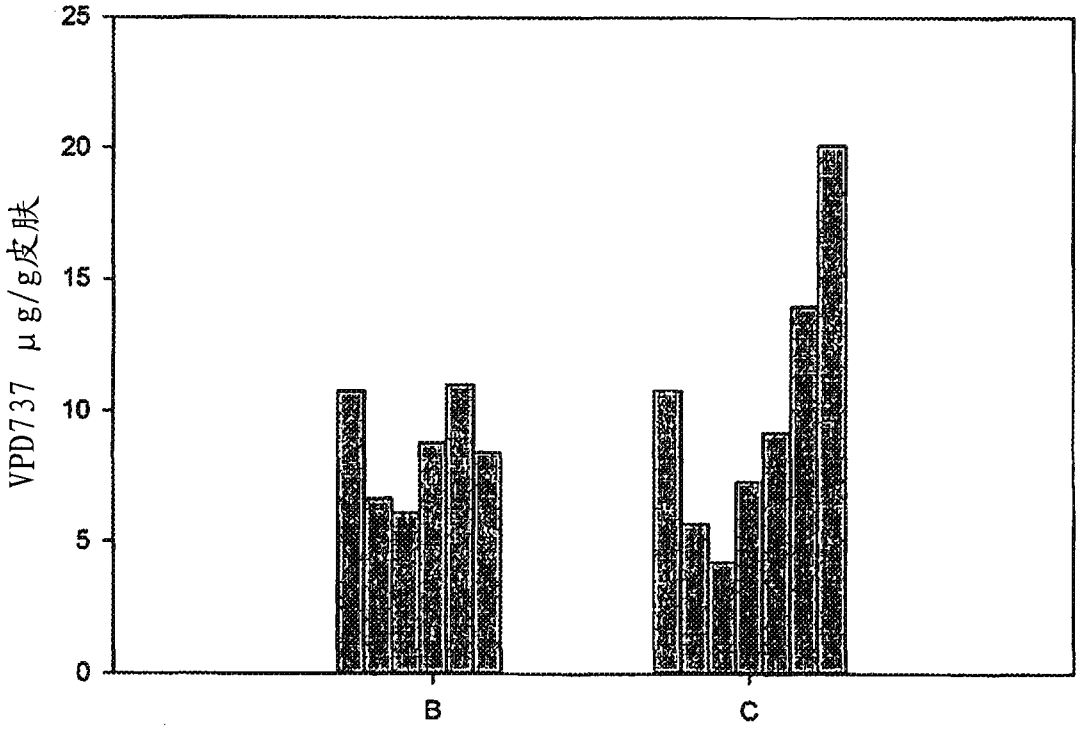


图4